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THE ROLE OF THE ADRENALS IN THE PRODUCTION OF RENAL CHANGES BY STH

HANS SELYE AND PIERRE BOIS

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Many of the effects of the "growth hormone" or somatotrophic hormone (STH) are not dependent upon the presence of the adrenals For example, STH stimulates skeletal growth, the proliferation of lymphatic tissues and inflammatory granuloma formation, even in completely adrenalectomized rats, provided that the animals receive adequate maintenance therapy in the form of salt supplements or corticoids It was unexpected to find, therefore, that the nephrotoxic effect of heavy overdosage with STH represents an exception in this respect This particular effect of STH cannot be obtained after complete adrenalectomy, even in rats optimally "conditioned" for nephrotoxic hormone actions (by unilateral nephrectomy and NaCl supplements) and maintained in perfect condition with adequate amounts of adrenocortical extract (Dontigny et al, 1946, Hall et al, 1946, Selye, 1946), cortisone (Selye, 1951a, b), cortisone plus desoxycorticosterone (Selye, 1952), or even ACTH, cortisone plus desoxycorticosterone (Selye and Bois, 1956a) High doses of desoxycorticosterone do produce nephrosclerosis, both in intact and in adrenalectomized rats, yet even the kidney-damaging effect, of such, in themselves, nephrosclerotic doses of the mineralocorticoid, can be aggravated by STH only if the adrenals are intact (Selye, 1951c), and not after bilateral adrenalectomy (Selye, 1953)

Whether STH exerts any adrenal-mediated action is still much debated, but all available data suggest that, unlike most of its classic actions, the nephrosclerotic effect of the "growth hormone" depends upon the functional integrity of adrenal tissue It would be difficult to explain otherwise that this particular effect is abolished after adrenalectomy, even if both gluco- and mineralocorticoids are supplied in abundant amounts by injection

It is the purpose of the present communication to report upon experiments designed to explore further 1) the dissociation among the STH effects which can be accomplished by complete adrenalectomy, and 2) the possible participation of adrenomedullary hormones in the production of nephrosclerosis with STH which had not yet been taken into consideration

METHOD

Two experimental series were performed in female *Sprague-Dawley rats* having an initial body-weight of 91–110 gm The animals were subdivided into lots of ten rats each, so that the mean initial body-weight was 101 gm in every group On the first day of the experiment the *left kidney was removed,* through a subcostal incision, under ether anesthesia, in the rats of both experimental series

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These experiments were performed with the aid of a grant from the Gustavus and Louise Pfeiffer Research Foundation

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and, in group 5 of the first experiment (cf. table 1), as well as in groups 3 and 4 of the second experiment (cf. table 2), bilateral *adrenalectomies* were performed at the same time.

All animals were fed exclusively on *Purina Fox Chow* and received *1% NaCl* to drink. Both *cortisol acetate* (COLA)* and *desoxycorticosterone acetate* (DOCA)* were administered subcutaneously (in the form of microcrystals in aqueous suspension), the daily dose being contained in 0.2 ml. of water. DOCA was given at the dose-level of 1 mg./day in both experiments. COLA was administered only in the second series and at the dose-level of 100 μg/day during the first 10 days, and 50 μg/day during the second 10 days of the experiment. *Adrenaline* (free compound)† and *noradrenaline* (levo-noradrenaline bitartrate monohydrate)* were injected subcutaneously twice daily, both at the dose-level of 100 μg per injection, in 0.2 ml. of sesame oil, in group 4 of the second experiment.

STH† was administered as a solution in 0.2 ml. of water subcutaneously twice daily, the individual dose being 1.5 mg. in the first, and 2 mg. in the second experiment. The reason for this difference in dosage was that the rats of the first series were maintained only with DOCA. This corticoid greatly synergizes the growth effect of STH, but does not adequately protect against death from hypoglycemia, which tends to be produced by this pituitary hormone in adrenalectomized animals. On the other hand, in the second experiment, in which COLA was also given, there was no danger of death from hypoglycemia, while the growth effect of STH could be expected to be partially counteracted by the catabolic and growth inhibitory action of the glucocorticoid.

The fluid intake of the animals was measured daily, as an indicator of the polyuria, which is a characteristic clinical sign of hormonally produced nephrosclerosis.

All the animals were killed with chloroform on the twenty-first day, their organs fixed in Susa mixture, weighed and histologically examined on paraffin sections stained with the PAS technique (McManus, 1948).

RESULTS

Although our two experimental series were performed at different times, they are so closely interrelated that the results may be discussed conjointly on the basis of the data summarized in tables 1 and 2.

In both tables the mean weights of the kidneys, heart, adrenals, thymus and spleen (in mg.), as well as the mean fluid intake of the last 10 days (in ml.), are listed together with their standard errors. The mean intensity of histologically detectable nephrosclerosis, myocarditis and periarteritis nodosa (the latter was examined only in the pancreatic vessels) has been assessed by appraising the intensity of the lesion in each rat in a scale of 0 to 3 plus and then dividing the total number of plusses by the number of experimental animals in the group.

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* Cortisol acetate ("Cortril") was generously supplied by the Pfizer Laboratories desoxycorticosterone acetate ("Cortate") by Schering Corporation, levo noradrenaline bitartrate by Winthrop Stearns of Canada, Ltd.

† Adrenaline was obtained from Brickman & Company, and STH ("Somatotropin") from The Armour Laboratories.

TABLE 1 *Summary of first experiment On the rôle of the adrenals in the production of renal and cardiovascular changes by STH in animals given DOCA*

Group	Treatment	Final Body Weight (gm.)	Kidney		Heart		Periarteritis*	Adrenals (mg.)	Thymus (mg.)	Spleen (mg.)	Fluid intake (ml./day)†	Mortality (%)
			mg	Nephrosclerosis*	mg	Myocarditis*						
1	None	159 ± 2.5	1297 ± 52.0	0	712 ± 23.7	0	0	15.8 ± 2.3	315 ± 18.0	500 ± 28.3	67 ± 2.5	0
2	STH	202 ± 2.7	1717 ± 70.8	<1	751 ± 19.7	0	0	61.8 ± 2.6	375 ± 27.8	720 ± 33.1	76 ± 1.3	0
3	DOCA	136 ± 3.1	1759 ± 89.2	1.8	672 ± 19.6	2.0	1	33.3 ± 1.6	183 ± 13.6	531 ± 51.7	133 ± 5.2	0
4	STH + DOCA	176 ± 11.1	2073 ± 172.1	3.0	801 ± 20.5	1.5	2	66.6 ± 3.0	118 ± 23.7	630 ± 81.2	209 ± 11.5	20
5	STH + DOCA + Adr X	105 ± 6.2	1958 ± 156.8	<1	837 ± 55.2	Trace	Trace	—	511 ± 18.1	705 ± 12.9	95 ± 6.0	70

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* Expressed in a scale of 0 to 3 plus, on the basis of histologic observations (periarteritis examined only in the pancreatic vessels)

† Mean of last ten days

TABLE 2 *Summary of second experiment on rôle of the adrenals in the production of renal and cardiovascular changes by STH in animals given DOCA + COL 1*

Group	Treatment	Final Body Weight (gm)	Kidney		Heart		Periarteritis*	Adrenals (mg)	Thymus (mg)	Spleen (mg)	Blood Pressure (mm/Hg)	Fluid Intake (ml/day)†	Mortality (%)
			mg	Nephrosclerosis*	mg	Myocarditis*							
1	DOCA + COLA	138 ± 4 1	1741 ± 95 6	1 8	762 ± 28 7	1 1	1 7	39 5 ± 0 7	279 ± 21 3	474 ± 31 5	159 ± 4 9	149 ± 6 9	0
2	STH + DOCA + COLA	170 ± 7 3	2266 ± 145 0	3 0	898 ± 39 8	2 2	1 8	53 4 ± 1 9	199 ± 16 9	725 ± 42 8	174 ± 6 4	171 ± 9 8	0
3	STH + DOCA + COLA + Adr X	183 ± 4 8	2287 ± 127 6	1 6	838 ± 20 1	0 9	0	—	412 ± 46 4	698 ± 52 2	159 ± 4 3	129 ± 9 3	0
4	STH + DOCA + COLA + Adr X + Adrenaline + Noradrenaline	134 ± 5 4	1216 ± 75 7	Trace	783 ± 29 4	Trace	0	—	205 ± 28 1	363 ± 28 5	125 ± 4 2	121 ± 6 2	20

* Expressed in a scale of 0 to 3 plus, on the basis of histologic observations on the pancreatic vessels

† Mean of last ten days

The *body-weight* was considerably increased by STH in all the rats of both series, with the exception of group 4 in the second experiment, in which the definitely toxic doses of adrenaline and noradrenaline counteracted the growth effect

In evaluating organ-weight changes we must take the great differences in the final body-weights into account It is evident, however, that in absolute terms the weight of the *kidneys* was increased in all STH-treated groups, with the notable exception of the severely damaged rats in group 4 of the second experiment The renal weight was greatest in rats injected with hormone combinations which included both STH and DOCA (with or without COLA) This renotrophic effect does not appear to depend upon the presence of the adrenals

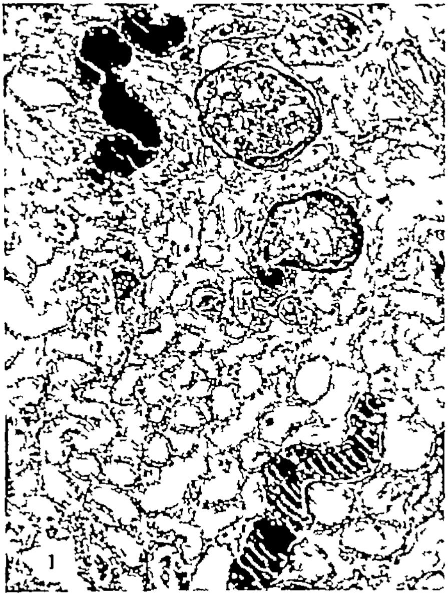
On the other hand, nephrosclerosis was only of moderate intensity in the rats of the first experiment, which received only STH (group 2) or DOCA (group 3), but very pronounced in the not adrenalectomized animals given conjoint treatment with both these hormones (group 4) Curiously, the adrenalectomized rats treated with both STH and DOCA (group 5) showed even less nephrosclerosis than the intact ones receiving DOCA alone (group 3)

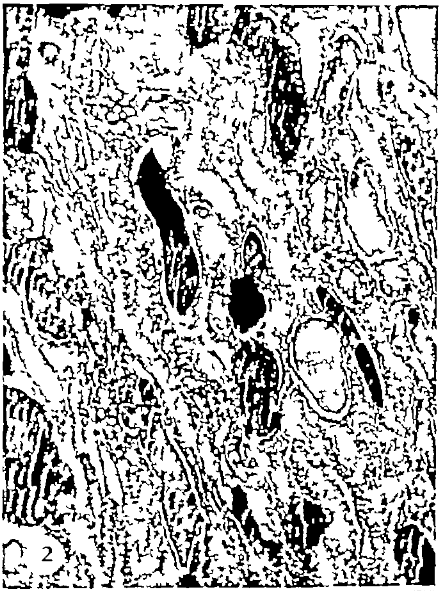
In the second experiment, in which very small amounts of COLA were given in addition to DOCA, the degree of nephrosclerosis was essentially the same in the corticoid-treated controls (group 1) as in the DOCA-treated rats of the previous series Here again, additional treatment with STH greatly aggravated the nephrosclerosis only in the presence of the adrenals (group 2), while after adrenalectomy the kidneys were even less damaged under the influence of combined treatment with DOCA, COLA and STH (group 3) than in the only corticoid-treated controls (group 1)

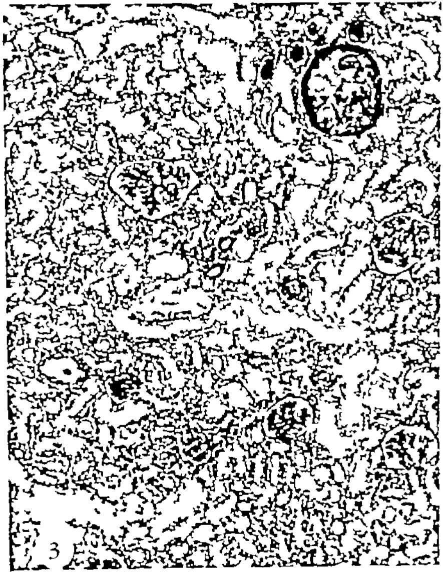
It is particularly noteworthy that combined treatment with definitely toxic and growth inhibitory doses of adrenaline and noradrenaline did not restore the ability of the adrenalectomized rats to respond to STH with nephrosclerosis, despite simultaneous maintenance therapy on adequate amounts of DOCA and COLA (group 4)

Histologically, the type of nephrosclerosis seen in these experiments was characterized by more or less diffuse hyalinization of the glomeruli and the afferent glomerular arterioles There was leakage of eosinophilic and PAS-positive material into Bowman's capsule, with the formation of hyalinized strongly PAS-positive casts in the tubules The larger renal arteries were less commonly affected (figs 1–4)

We should like to call special attention the very frequent occurrence of dense intensely PAS-positive aggregates of rods and blocks of fibrinoid material between the renal tubules These were often found even in rats treated with STH alone and in adrenalectomized animals receiving STH in combination with DOCA The fibrinoid blocks do not appear to be spacially connected with blood-vessels, but seem to arise from the intertubular connective tissue itself (figs 5 and 6) It is also noteworthy that the regional lymph nodes of the kidney and adrenal were usually transformed into hemolymph nodes (fig 7) in the not adrenalectomized animals receiving combined treatment with STH and DOCA (group 4 of first and group 2 of second experiment), while this was not the case







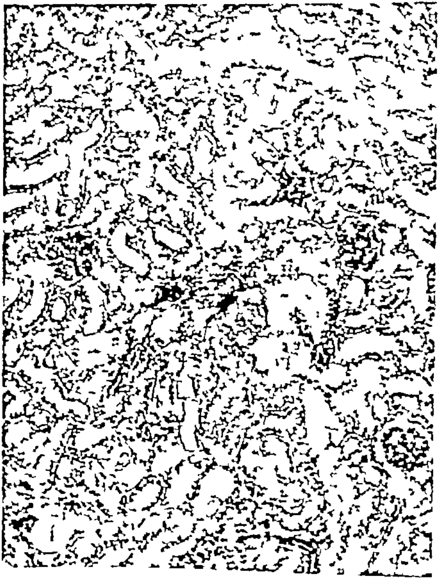


FIG 1 Renal changes in not adrenalectomized rat treated with STH plus DOCA (group 4) Note enlargement and hyalinization of glomeruli with formation of hyalin casts (PAS × 75)

FIG 2 Region from medullary part of kidney of rat whose renal cortex is shown in figure 1 Here hyalin casts are particularly numerous (PAS × 75)

FIG 3 Renal cortex of rat treated with DOCA alone (group 3) Note that changes are essentially similar to those seen in figure 1, but considerably slighter in degree (PAS × 75)

FIG 4 Renal cortex of adrenalectomized rat treated with STH and DOCA (group 5) Here renal cortex is essentially normal and quite different in appearance from depicted in figure 1 although hormone treatment was same Only upon close inspection do we note a few particularly PAS positive blocks between tubules in center of the field (PAS × 75)

in similarly treated but adrenalectomized animals (group 5 of first and groups 3 and 4 of second experiment)

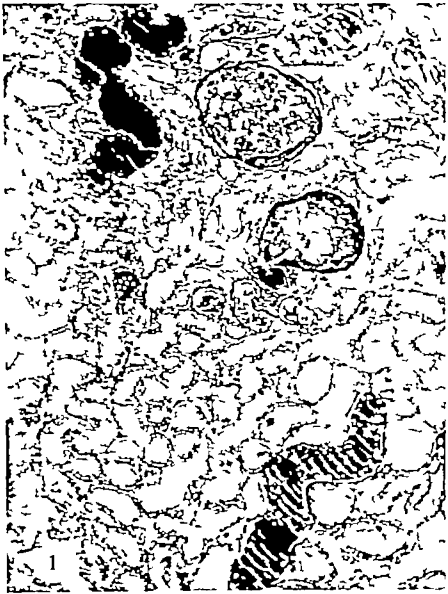
The weight of the *heart* was more or less significantly increased in all STH-treated groups and, in this respect, adrenalectomy failed to block the effect of the growth hormone On the other hand microscopic evidence of myocarditis ran approximately parallel to the severity of nephrosclerosis in all groups The histologic changes characteristic of this kind of myocarditis somewhat resemble the picture of cardiac periarteritis nodosa and rheumatic heart disease as it occurs in man Usually, large amounts of homogeneous hyalin material are deposited underneath the intima of the coronary arteries and gradually the media and adventitia become involved in an inflammatory process In addition, there develop small nodules (reminiscent of the "Aschoff-bodies" of rheumatic fever) within the myocardium These nodules consist of a central, partially hyalinized, strongly PAS-positive deposit, surrounded by proliferating granuloma cells, some of which are polynuclear (fig 8)

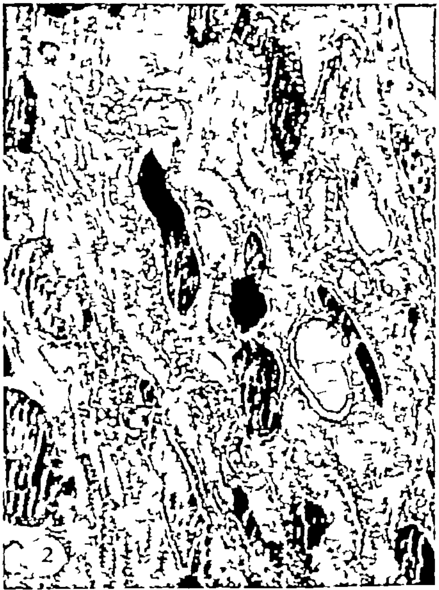
Periarteritis nodosa in the pancreatic vessels was observed quite regularly in the rats treated with DOCA (group 3 of first experiment) or DOCA plus STH (group 4 of first experiment) This change appears to have been almost completely prevented by adrenalectomy and, in any event, the aggravation of periarteritis nodosa by STH after DOCA treatment was no longer manifest in the absence of the adrenals (group 5 of first experiment) In the rats which, in addition to DOCA and STH, were also treated with COLA (group 3 of second experiment), the prevention of periarteritis nodosa by adrenalectomy was even more complete and treatment with the adrenalines did not affect this (group 4 of second experiment)

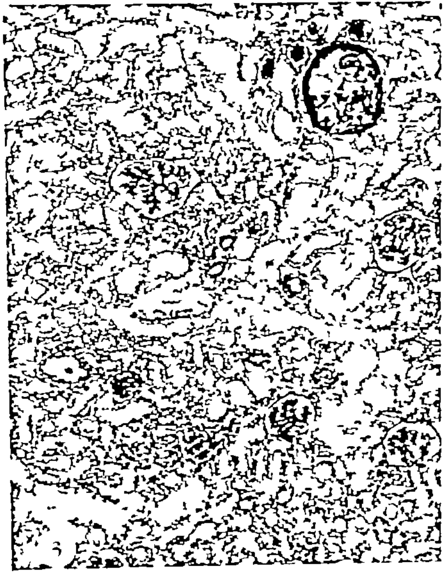
The *adrenals* showed the customary increase in weight following STH administration (group 2 of first experiment), even in the case of simultaneous treatment with DOCA (group 4 of first experiment), or DOCA and COLA (group 2 of second experiment)

The *thymus* and *spleen* became enlarged under the influence of STH in the adrenalectomized rats maintained on DOCA (group 5 of first experiment), or on DOCA plus COLA (group 3 of second experiment) In all the intact rats, as well as in those adrenalectomized animals which were simultaneously treated with DOCA, adrenaline and noradrenaline (group 4 of second experiment), this effect was absent We assume that it was counteracted by the thymolytic and splenolytic actions of endogenous glucocorticoids produced under the influence of the stress of nephrosclerosis and myocarditis in the first case, and the particularly lymphotoxic combination of a glucocorticoid with adrenergic hormones in the animals given COLA, adrenaline and noradrenaline

The *fluid intake* and polyuria roughly paralleled the intensity of the nephrosclerosis in the various groups In any event, it is quite obvious that adrenalectomy abolished the diuretic action of STH under these circumstances, even when both types of corticoids and both types of adrenalines were administered in doses well in excess of mere substitution therapy







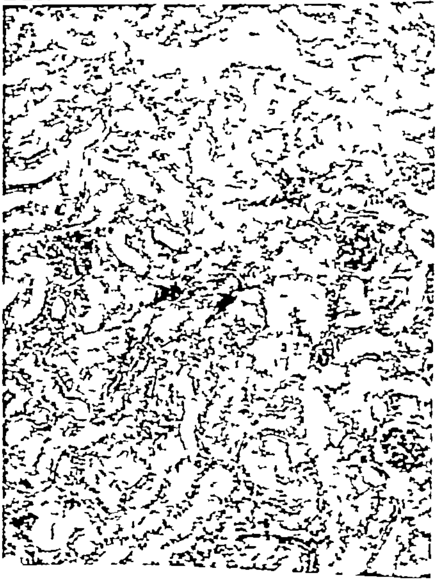


FIG 1 Renal changes in not adrenalectomized rat treated with STH plus DOCA (group 4) Note enlargement and hyalinization of glomeruli with formation of hyalin casts (PAS × 75)

FIG 2 Region from medullary part of kidney of rat whose renal cortex is shown in figure 1 Here hyalin casts are particularly numerous (PAS × 75)

FIG 3 Renal cortex of rat treated with DOCA alone (group 3) Note that changes are essentially similar to those seen in figure 1 but considerably slighter in degree (PAS × 75)

FIG 4 Renal cortex of adrenalectomized rat treated with STH and DOCA (group 5) Here renal cortex is essentially normal and quite different in appearance from depicted in figure 1 although hormone treatment was same Only upon close inspection do we note a few particularly PAS positive blocks between tubules in center of the field (PAS × 75)

in similarly treated but adrenalectomized animals (group 5 of first and groups 3 and 4 of second experiment)

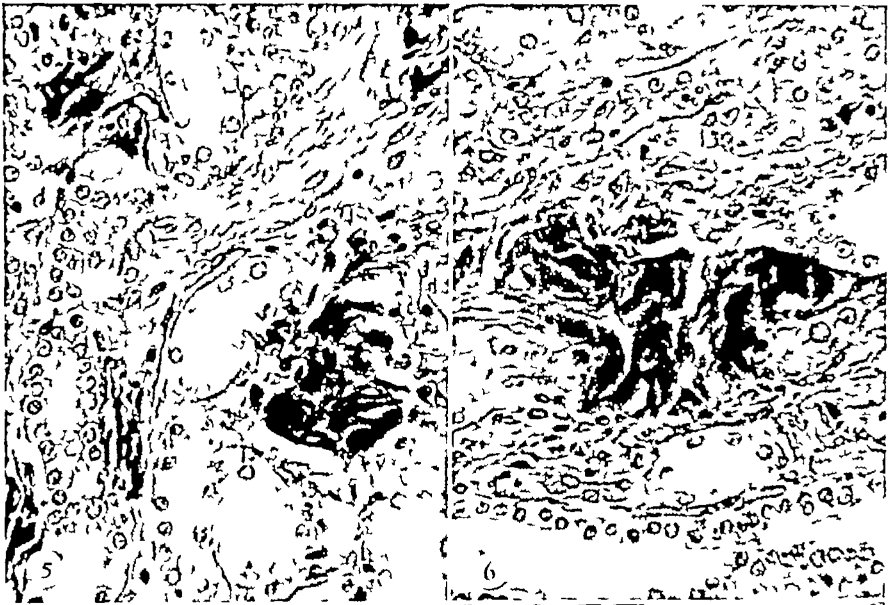
The weight of the *heart* was more or less significantly increased in all STH-treated groups and, in this respect adrenalectomy failed to block the effect of the growth hormone On the other hand microscopic evidence of myocarditis ran approximately parallel to the severity of nephrosclerosis in all groups The histologic changes characteristic of this kind of myocarditis somewhat resemble the picture of cardiac periarteritis nodosa and rheumatic heart disease as it occurs in man Usually, large amounts of homogeneous hyalin material are deposited underneath the intima of the coronary arteries and gradually the media and adventitia become involved in an inflammatory process In addition, there develop small nodules (reminiscent of the "Aschoff-bodies' of rheumatic fever) within the myocardium These nodules consist of a central, partially hyalinized, strongly PAS-positive deposit, surrounded by proliferating granuloma cells, some of which are polynuclear (fig S)

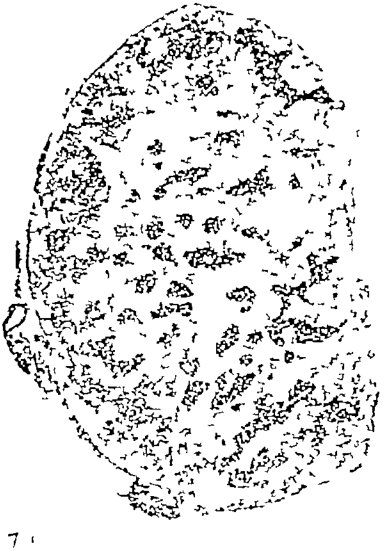
Periarteritis nodosa in the pancreatic vessels was observed quite regularly in the rats treated with DOCA (group 3 of first experiment) or DOCA plus STH (group 4 of first experiment) This change appears to have been almost completely prevented by adrenalectomy and, in any event the aggravation of periarteritis nodosa by STH after DOCA treatment was no longer manifest in the absence of the adrenals (group 5 of first experiment) In the rats which, in addition to DOCA and STH, were also treated with COLA (group 3 of second experiment), the prevention of periarteritis nodosa by adrenalectomy was even more complete and treatment with the adrenalines did not affect this (group 4 of second experiment)

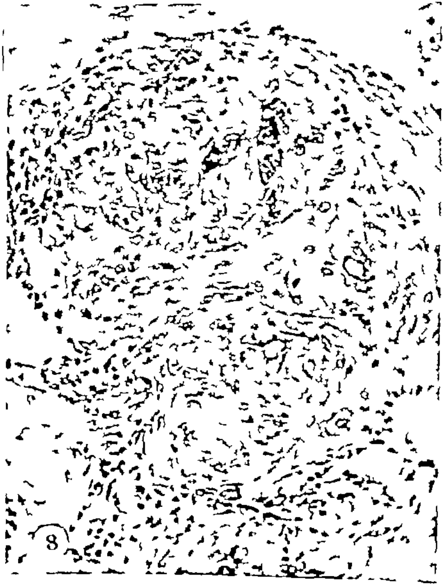
The *adrenals* showed the customary increase in weight following STH administration (group 2 of first experiment), even in the case of simultaneous treatment with DOCA (group 4 of first experiment), or DOCA and COLA (group 2 of second experiment)

The *thymus* and *spleen* became enlarged under the influence of STH in the adrenalectomized rats maintained on DOCA (group 5 of first experiment) or on DOCA plus COLA (group 3 of second experiment) In all the intact rats, as well as in those adrenalectomized animals which were simultaneously treated with DOCA, adrenaline and noradrenaline (group 4 of second experiment), this effect was absent We assume that it was counteracted by the thymolytic and splenolytic actions of endogenous glucocorticoids produced under the influence of the stress of nephrosclerosis and myocarditis in the first case, and the particularly lymphotoxic combination of a glucocorticoid with adrenergic hormones in the animals given COLA, adrenaline and noradrenaline

The *fluid intake* and polyuria roughly paralleled the intensity of the nephrosclerosis in the various groups In any event it is quite obvious that adrenalectomy abolished the diuretic action of STH under these circumstances, even when both types of corticoids and both types of adrenalines were administered in doses well in excess of mere substitution therapy







FIGS 5 and 6 Higher magnification showing the intensely PAS positive intertubular hyalin blocks in a rat of group 2 which was treated with STH alone (PAS × 400)

FIG 7 Renal lymph node of not adrenalectomized rat treated with STH and DOCA Sinusoids are filled with blood, so that organ is actually transformed into a hemolymph node It will be recalled that this change is also prevented by adrenalectomy (PAS × 40)

FIG 8 Granulomatous nodule in subendocardial tissue of not adrenalectomized rat treated with STH and DOCA Note intensely PAS positive hyalin material in center of nodule (PAS × 200)

An important *mortality rate* (70 per cent) was seen only in the STH-treated adrenalectomized animals which received exclusively mineralocorticoid maintenance treatment (group 5 of first experiment) It is precisely because of this high mortality that we repeated the experiment adding a small amount of COLA to the maintenance therapy in the second series As expected this resulted in the survival of all adrenalectomized rats treated with STH (group 3 of second experiment)

The two deaths in the similarly treated animals which in addition also received adrenaline and noradrenaline (group 4 of second experiment), were manifestly due to overdosage with the adrenergic hormones Autopsy revealed the marked hemorrhagic lung-edema characteristic of intoxication with adrenalines and even the survivors in this group showed obvious clinical signs of adrenaline-overdosage during the entire period of observation

DISCUSSION

The results of our two experimental series appear to support the view that a dissociation among the STH effects can be accomplished by complete adrenalectomy For example, the influence of STH upon somatic growth in general and its ability to stimulate the development of lymphatic organs in particular were not prevented by complete suprarenalectomy In fact a given dose of STH caused more pronounced thymus enlargement in adrenalectomized animals (whether maintained on DOCA alone or on DOCA plus COLA) than in corresponding intact rats This is presumably due to the fact that endogenous glucocorticoids can counteract the thymolytic effect of STH only in rats whose adrenals are intact On the other hand the morbid lesions normally induced by heavy STH overdosage in the kidney and heart are completely prevented by adrenalectomy

The experiments presented here confirm earlier observations which showed that STH increases the nephrosclerotic action of DOCA This was found to be the case also when renal damage is produced by conjoint treatment with DOCA and COLA. However even the renal damage occasioned by large amounts of corticoids (in quantities sufficient to produce renal damage in themselves) was not further aggravated by STH treatment in the absence of the adrenals This shows that for its nephrotoxic activity STH required the presence of adrenal tissue and not merely the conditioning influence of the life-maintaining corticoids

The question still remained whether STH exerts its nephrotoxic effect through some new type of corticotrophic action or whether its ability to produce renal damage depends upon the presence of adrenomedullary hormones Our second experimental series appears to have eliminated the latter alternative Even in the presence of in themselves toxic amounts of a glucocorticoid a mineralocorticoid adrenaline and noradrenaline STH produced no morbid changes in the kidney (nor incidentally in the heart or the vessels)

Blood pressure measurements were performed only in the second experiment

They suggest that, simultaneously with the aggravation of the renal lesions, STH augmented the pressor effect of combined treatment with DOCA and COLA only in the presence of the adrenals However, some of the rats given STH in addition to the corticoids were severely damaged Hence, their blood pressure dropped and the resulting variability increased the standard error to such an extent that the difference between groups 1 and 2 is not statistically significant In any event, it is obvious, however, that after adrenalectomy the pressor action of STH was also abolished Curiously, in the adrenalectomized rats given combined treatment with STH, DOCA, adrenaline and noradrenaline, the blood pressure likewise failed to rise This may be due to the fact that we had to use definitely toxic doses of the adrenalines to prove that after adrenalectomy, even in the presence of extreme overdosage with medullary hormones, STH does not exert its nephrotoxic and vasotoxic effects Although the animals so treated were not actually in shock, it is probable that they were sufficiently damaged to interfere with the normal pressor action of the adrenergic hormones

In view of these findings it is difficult to escape the conclusion that some effects of STH are direct, while others are mediated through the adrenals and not merely dependent upon the presence in the body of the principal adrenocortical or medullary hormones

STH does undoubtedly possess some corticotrophic effect, since it stimulates adrenal growth in intact animals But this was tentatively ascribed to the secondary stimulation of endogenous ACTH production by the pituitary, since no comparable adrenal hypertrophy could be obtained by STH treatment in the hypophysectomized rat (Selye and Heuser, 1955/56) Yet a secondary endogenous ACTH secretion does not suffice to explain our observations, as it is not possible to reproduce the renal and cardiovascular effects of STH overdosage by ACTH treatment, either in intact or in hypophysectomized rats

These findings—as well as the great enhancement of the nephrotoxic and vasotoxic actions of STH by simultaneous treatment with DOCA—suggest that certain effects of the somatotrophic hormone depend upon a special type of corticotrophic action It is possible, for instance, that, under the influence of STH, DOCA is transformed into some much more active mineralocorticoid in the adrenal cells Earlier experiments showed, for example, that 2-methyl-9(α)-fluorocortisol possesses more than 100 times the nephrotoxic and vasotoxic potency of desoxycorticosterone (Selye and Bois, 1956b) There is no reason to suspect that such methylated halocorticoids can arise in the adrenal, but the high activity of these synthetic steroids proves that the DOCA molecule is still capable of considerable activation in this respect Further experiments will have to show whether STH can, in fact, effect such an activation, for instance, in perfused adrenals or in adrenal slices incubated with DOCA as a substrate

SUMMARY

Experiments on rats sensitized to mineralocorticoid hormone actions by unilateral nephrectomy and a high sodium intake revealed that

1) The nephrotoxic and vasotoxic actions of intense overdosage with somato-

trophic hormone (STH) are wholly dependent upon the presence of the adrenals In this respect they differ from other actions of the somatotrophic hormone for instance its ability to stimulate somatic growth and the development of the thymicolymphatic apparatus Consequently adrenalectomy induces a qualitative change in the picture of STH overdosage it selectively abolishes the renal and cardiovascular effects without notably interfering with most of the other manifestations

2) Treatment with large doses of desoxycorticosterone acetate (DOCA) alone or in combination with cortisol acetate (COLA) intensifies the nephrotoxic actions of STH in the presence but not in the absence of the adrenals Even the effects upon the kidney of in themselves nephrotoxic amounts of the corticoids cannot be further aggravated by simultaneous STH treatment

3) Adrenalectomy does not block the nephrotoxic and vasotoxic actions of STH by eliminating the adrenal medulla because these effects do not manifest themselves in STH-treated adrenalectomized rats even if they are concurrently treated with very high doses of DOCA COLA adrenaline and noradrenaline

4) The possibility is discussed that the adrenal-dependent STH actions may be due to an activation of DOCA-like compounds in the adrenals under the influence of somatotrophic hormone

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ADRENAL CYST

REGINALD A HANCOCK

Benign adrenal cysts are considered rare Of the 81 cases reported, the majority were noted at necropsy The adrenal cysts encountered at surgery are of sufficient size to be important surgically in contrast to the smaller silent cyst seen at postmortem examination These cysts do not present any characteristic clinical picture Their effects are purely mechanical (sense of pressure or palpable mass) and there are no endocrine disturbances A suspicion of the disease is based on the urographic and aortographic findings with confirmation at operation These cysts often present a diagnostic problem, hence the following case is considered worthy of presentation

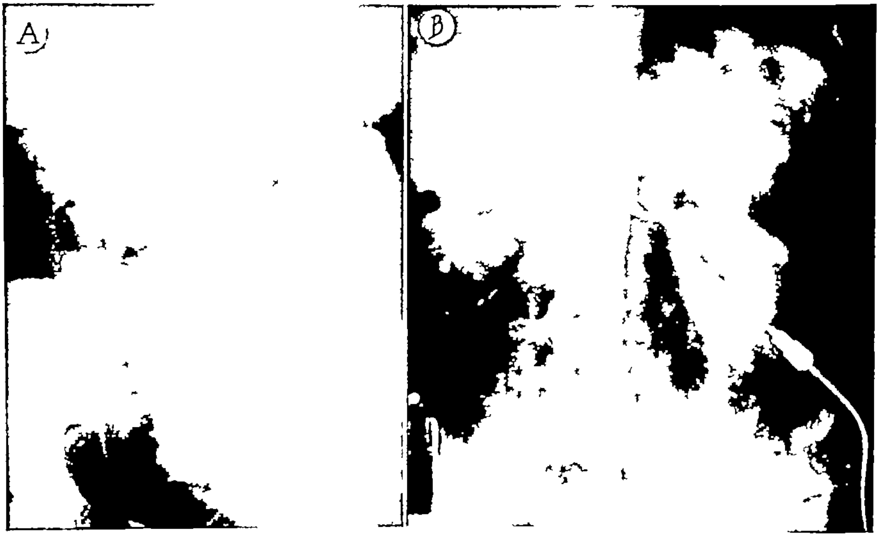

FIG 1 *A*, left kidney displaced downward by suprarenal mass *B*, displaced left kidney and adrenal cyst with its blood supply

CASE REPORT

A white woman, E M, No B770, aged 51 years, who had been a known diabetic for 10 years, was admitted to the Presbyterian Hospital in May 1954, with a history of weakness Physical examination revealed a palpable mass in her left flank The laboratory studies were within normal limits, except for a blood sugar of 206 mg Retrograde pyelograms revealed downward displacement of the left kidney without distortion of the calcyces (fig 1, *A*) A translumbar aortogram again showed the displacement of the left kidney with a translucent mass above the kidney demonstrating its arterial blood supply (fig 1, *B*) Surgical exposure, using a left post-lumbar rib resecting incision, revealed the thin walled adrenal cyst The cyst was not attached to the kidney but the upper pole of the kidney was indented by the pressure from the cyst It was readily removed intact with the adrenal gland adherent on its medial surface (fig 2, *A*)

Read at annual meeting Southeastern Section of American Urological Association, Hollywood Beach, Fla, March 25-29, 1956

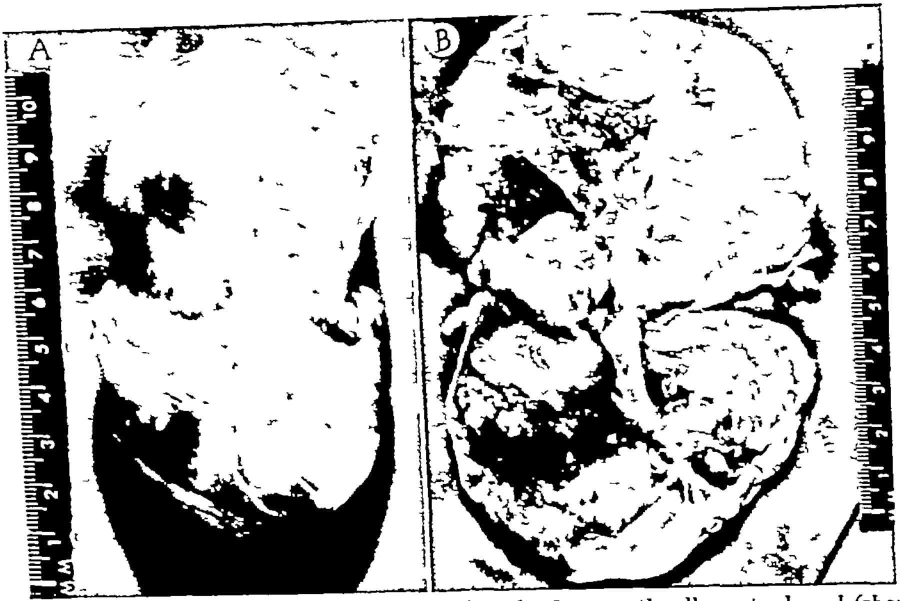

FIG 2 A adrenal cyst intact measures 10 by 7 by 6 cm with adherent adrenal (shown only on color film) *B*, loculated adrenal cyst contained 70 cc amber fluid

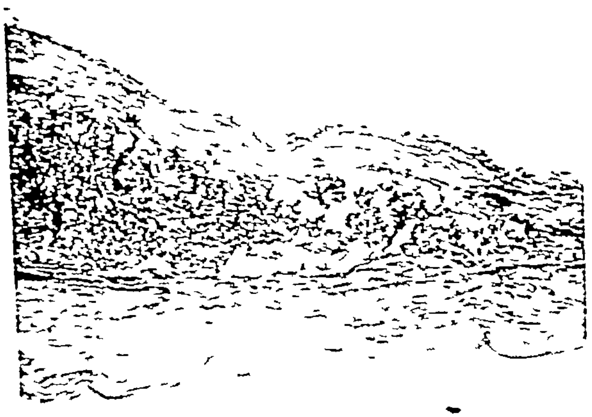

FIG 3 Microscopic section revealed adrenal cortex peripheral to cyst wall

Examination of the specimen by Dr R S Totten revealed a multiloculated thin walled cystic mass measuring 10 by 7 by 6 cm The external surface was smooth and had a few tags of bright yellow fat Adherent to one surface was a thin, Y shaped deposit of pale yellowish-orange tissue resembling adrenal cortex The mass was fluctuant and contained 70 cc of clear amber fluid and soft, gelatinous material adherent to the lining of the cavity It was divided into multiple connecting loculi See figure 2, *B*

Microscopic examination Multiple sections of the cyst showed a lining of laminated collagenous material (fig 3) Peripheral to this layer in several sections were remnants of adrenal cortex No epithelial cells were seen within the cyst

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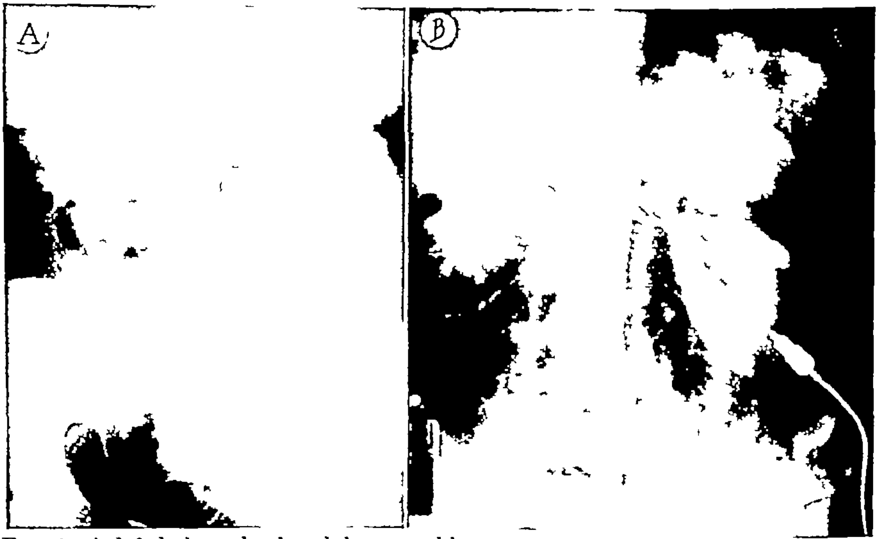

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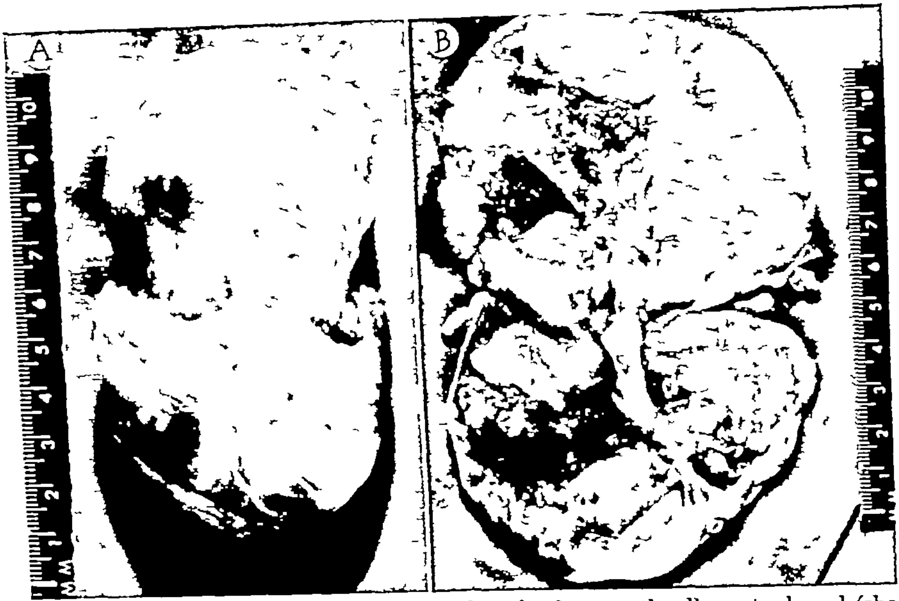

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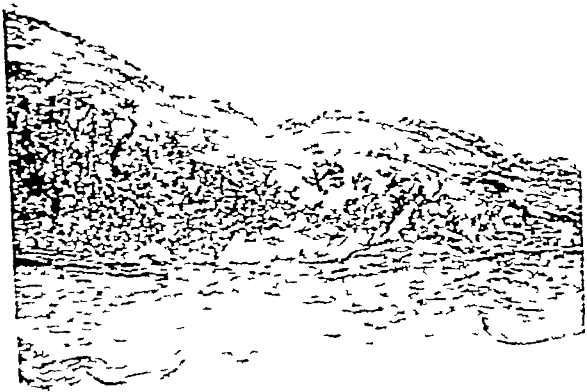

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SURGICAL TREATMENT OF SEROUS CYST OF THE KIDNEY

GEORGE C PRATHER

The purpose of this paper is to present a simplified surgical technique for the treatment of serous cyst of the kidney along with followup observations indicating no postoperative recurrence of the cyst

The treatment of serous cyst of the kidney may be expectant if the differentiation from solid tumor is certain, although I personally doubt that a correct diagnosis can be made consistently without surgical inspection

Aspiration of the cyst as a form of treatment has been suggested by Dean in selected cases The fear of overlooking the presence of solid tumor associated with the cyst has prevented me from adopting the aspiration technique

I know of one elderly woman who apparently cured herself by falling over the back of a chair, striking the flank area and rupturing the cyst Although effective in eliminating the mass, we cannot recommend this program for general use

The commonly accepted surgical treatment of serous cyst of the kidney is complete excision or enucleation of the cyst, or destruction of the epithelium of the cyst wall on the surface of the kidney by chemicals or electrocoagulation following excision of the parietal portion of the cyst These operations have been proposed in the excellent standard urological texts of Watson and Cunningham, Young, Hinman, Cabot, McCrae, Dodson, Rolnick, and Campbell (Deming chapter), and in comprehensive papers by O'Conor, Mathé, and Shivers and Axilrod

Probably the basis for the recommendation of excision or destruction of the visceral epithelium of the cyst in contact with the kidney is the elimination of any continued secretion by remaining cyst wall which might lead to recurrence of the cyst

The surgical removal of the visceral wall of the cyst can be a bloody procedure The destruction of the visceral layer by chemicals or electrocoagulation can produce an intense reaction which may lead to postoperative discomfort, edema of the surgical incision or sterile abscess

I do not believe it is necessary or even advisable to treat the visceral layer of the cyst on the surface of the kidney The basis for this statement is uniform success with simple excision of the parietal cyst wall over a period of 25 years and no known recurrence in the cases so treated The logic of the operation may be somewhat similar, although by no means identical to the surgical correction of hydrocele Certainly no one attempts to remove or destroy the visceral tunica vaginalis on the surface of the testis during operation for hydrocele

The technique is not new with me I learned it from the late E Granville Crabtree, and I believe the procedure has been used by some urologists for years Keyes indicated that the cyst may be permanently cured by "excising the top of the cyst " Colby's text reflects this opinion, and Priestley agrees that it is not necessary to remove or destroy the portion of the cyst wall attached to renal substance

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The operation described herein and illustrated in figure 1 consists of the following steps exposure of the kidney through the incision of choice separation of perirenal fat from the area of the cyst, puncture and aspiration of cyst fluid inspection of the interior of the cyst for possible tumor, excision of the parietal portion of the cyst wall to within 1 cm of the renal cortex, ligation of bleeding

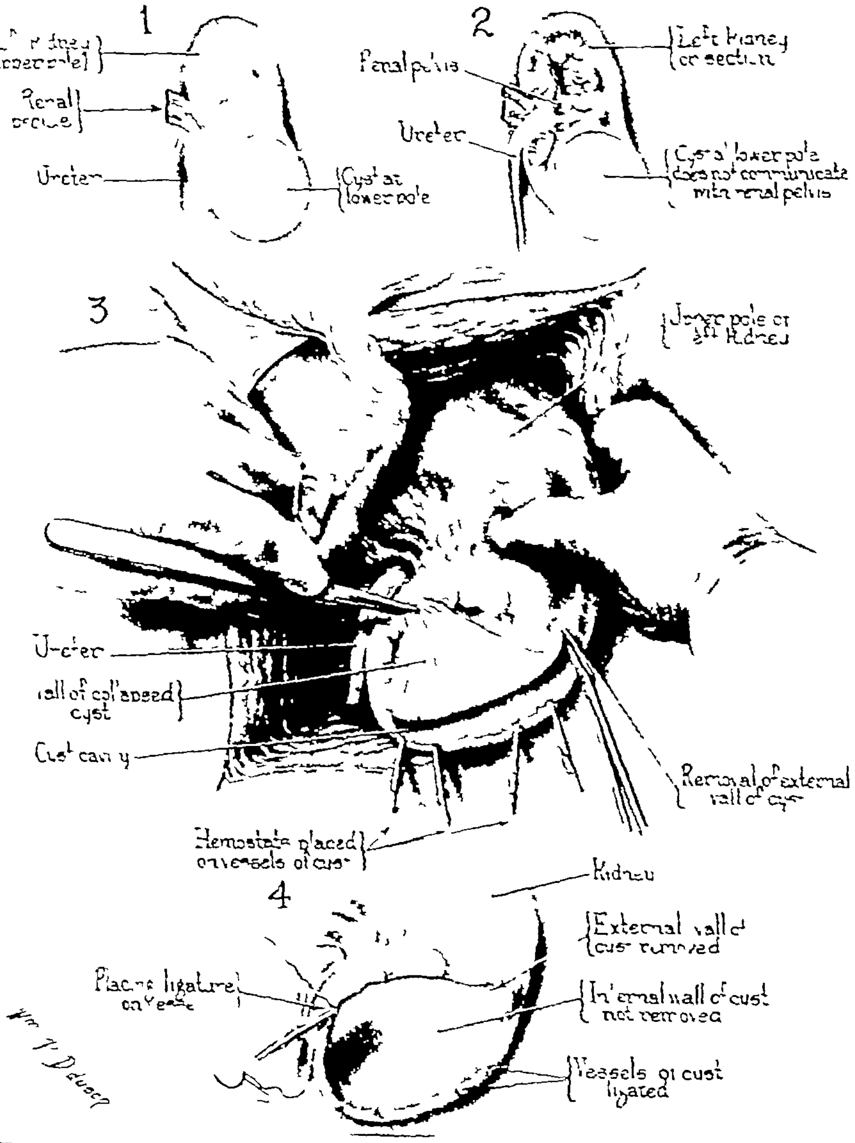
1
Left kidney (lower pole)
Renal pelvis
Ureter
Cyst at lower pole
2
Renal pelvis
Left kidney on section
Ureter
Cyst at lower pole does not communicate with renal pelvis
3
Lower pole of left kidney
Ureter
Wall of collapsed cyst
Cyst cavity
Removal of external wall of cyst
Hemostats placed on vessels of cyst
4
Kidney
External wall of cyst removed
Place ligature on vessel
Internal wall of cyst not removed
Vessels of cyst ligated
Wm P Didusch

Fig 1 Findings and operative technique for serous cyst of kidney 1, Unopened cyst at lower pole of kidney 2, Diagrammatic sketch of hypothetically bisected kidney with interior of cyst exposed (This is not done at operation) 3 External (parietal) wall of cyst excised close to cortex of kidney 4 Bleeding points at edge of cyst margin controlled by ligature or suture No treatment to visceral cyst membrane

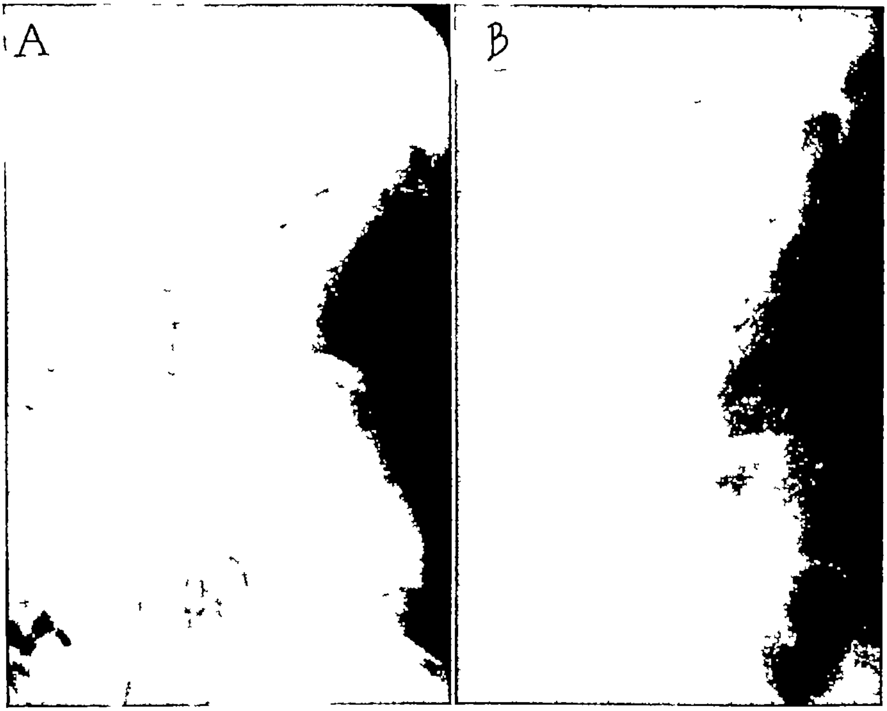

FIG 2 *A*, preoperative retrograde pyelogram in January 1947 Serous cyst at upper pole of left kidney, and stone in lower left ureter are shown *B*, postoperative excretory urogram in July 1953 (renal margin retouched), shows no recurrence of cyst or stone

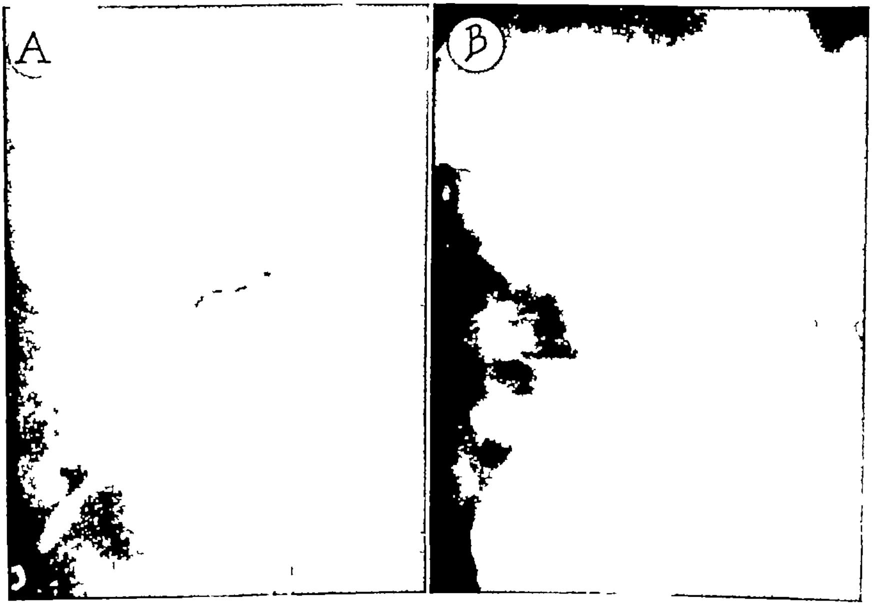

FIG 3 *A*, preoperative retrograde pyelogram shows two large serous cysts of the right kidney, November 1951 *B*, postoperative roentgenogram of renal areas December 1952, shows normal right kidney outline

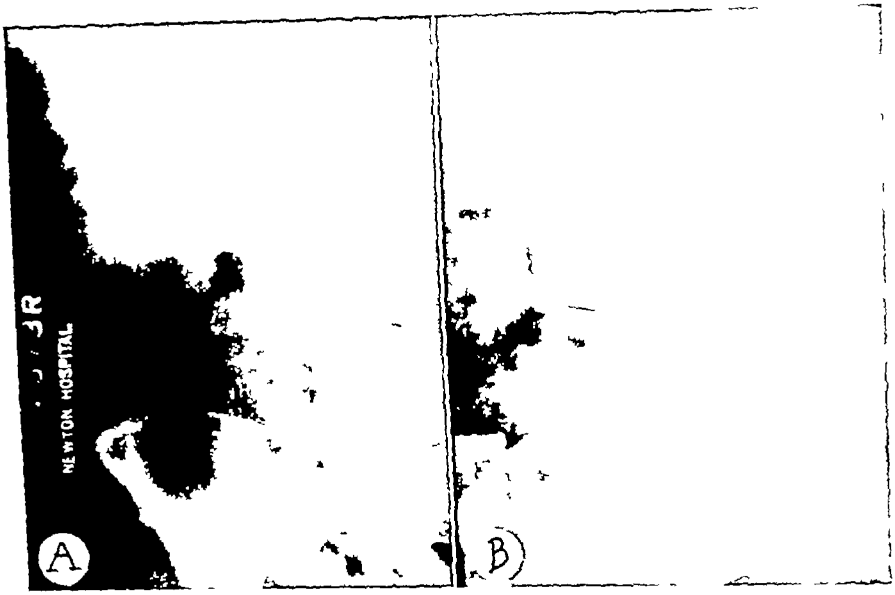

Fig 4 A, preoperative retrograde pyelogram, October 1946, shows large serous cyst at lower pole of right kidney *B*, postoperative excretory urogram (renal margin retouched) April 1953, shows normal lower pole of right kidney

points, and closure of the muscle layers and skin, with Penrose drain placed to the perirenal tissue

In order to have evidence by roentgenogram as well as by physical examination that no recurrence of the cyst had taken place, six of our patients operated upon in this manner were studied 1 to six years later by means of plain roentgenogram of the renal areas or by intravenous urography Illustrative findings may be observed in figures 2 to 4 All patients are asymptomatic and none show evidence of recurrence of cyst

The operation described is simple, avoids the hazards of more extensive renal surgery and permits rapid recovery

SUMMARY

Simple excision of the parietal wall of the serous cyst is advocated It is not necessary to remove or destroy that portion of the cyst wall which is in contact with the cortex of the kidney Followup studies of some of our patients show no recurrence of the cyst

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COMPLICATIONS OF NEPHROLITHOTOMY WITH SPECIAL REFERENCE TO SECONDARY HEMORRHAGE

WILLIS P JORDAN JR AND GILBERT C TOMSKEY

From the Veterans Administration Hospitals, New Orleans Louisiana, and Lake City, Florida, and the Department of Urology, Tulane University of Louisiana School of Medicine, New Orleans

The medical literature contains little statistical data concerning the incidence of the two most serious complications of nephrolithotomy, namely, secondary hemorrhage and urinary fistula In the 1,482 operations collected from the literature by Abeshouse and Lerman, which covered the period from 1922 to 1929, the incidence ranged from 3 5 per cent, in Tardo's 316 operations, to 33 3 per cent in Papin's 12 operations, and was 10 5 per cent for the whole series In Gottstein's 215 collected cases, which Abeshouse and Lerman mention but do not include in their tabulated data, the mortality rate was 11 2 per cent, and secondary nephrectomy was necessary in 87 cases, 40 per cent It should be noted, however, that these figures concern a period in which neither modern surgical techniques nor modern antibiotics were employed

Joly reported 2 cases of severe secondary hemorrhage in 67 nephrolithotomies performed at St Peter's Hospital, Dublin, during the period 1915–1924, but reported in 1940 that his personal experience included a total of 5 cases, though he did not state in how many operations they had occurred In 3 cases, one of which was fatal, secondary nephrectomy was necessary to control the bleeding, and in the other 2 cases, in which bleeding ceased spontaneously, the kidney was later removed for continued sepsis

In 1,247 nephrolithotomies collected by Abeshouse and Lerman, the incidence of persistent urinary fistula was 12 5 per cent, the range extending from 3 65 per cent in Brongersma's 82 cases to 21 1 per cent in Tardo's 288 operations

The impetus for this study of the complications of nephrolithotomy was the occurrence of intractable hemorrhage in 2 cases within a short period of time Our series consists of 75 operations performed at the Veterans Administration Hospitals at New Orleans and Lake City, Florida, and Charity Hospital of Louisiana at New Orleans during the years 1950–1955 inclusive About two-thirds of the operations were performed at Charity Hospital

Our analysis was chiefly limited to those complications which arise from the special character of the operation The 2 cases of atelectasis and the 4 cases of thrombophlebitis, all of which required secondary surgery in the form of either superficial femoral ligation or ligation of the vena cava, might have followed any variety of major surgery and need no special discussion The single death in the series was caused by pulmonary tuberculosis and was not attributable to the type of surgery performed

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Read at annual meeting Southeastern Section of American Urological Association, Hollywood Beach, Fla , March 25–29, 1956

ANALYSIS OF CASES

The complications referable to the renal surgery in these 75 cases were as follows

Secondary hemorrhage occurred in 7 cases, 9 0 per cent, which is of the same order as the 10 5 per cent reported by Abeshouse and Lerman in their 1,482 collected cases The hemorrhage was controlled by conservative measures in 2 cases but nephrectomy was required in the other 5

Persistent urinary fistula occurred in 6 cases, all instances of severe infection in which drainage by nephrostomy had been necessary for long periods of time The fistula closed spontaneously in 5 cases, but the remaining patient required nephrectomy for a persistent renocutaneous fistula

Perinephric abscess occurred in 2 cases In 1 instance, in which the infection was Proteus in character, surgical drainage was sufficient In the other case, in which infection was caused by Staphylococcus aureus, nephrectomy was necessary

In 7 cases recurrent calculus formation was a delayed complication, and nephrectomy was required in 4 instances In 2 other cases the kidney became essentially functionless after operation

In all, the complications which arose because of the special type of surgery performed in these 75 cases numbered 24, almost 33 per cent In 11 instances nephrectomy was required, either immediately, as a lifesaving measure, or at some time after operation Two other patients suffered, in effect, a physiologic nephrectomy, because they were left with functionless kidneys In Joly's opinion, if every patient who had recovered spontaneously from secondary hemorrhage could be examined at a later date, the kidney would be found to be practically useless Such an investigation, as he states, does not seem to have been carried out

This is a high incidence of complications and poor results for an operation that is designed to be conservative and to preserve function It supports the statement of Joly, which is concurred in by Abeshouse and Lerman, that nephrolithotomy is attended by such risks from secondary hemorrhage that the operation should be employed only when it is quite impossible to remove the calculus through an incision in the renal pelvis

URINARY FISTULA

Urinary fistula is usually the result of gross infection, prolonged drainage by nephrostomy, or failure to recognize the existence of a ureteral obstruction In Joly's opinion, the principal cause of persistent fistula is the attempt to remove stones by a conservative technique in cases in which nephrectomy is indicated There is no doubt in our own minds that a more careful evaluation of the status of the kidney before the precise operation was decided upon would increase the incidence of nephrectomy but would greatly reduce the incidence of urinary fistulas caused by failure to employ the radical operation when it is indicated

SECONDARY HEMORRHAGE

Secondary hemorrhage, the most frequent and most serious complication of nephrolithotomy, usually occurs between 7 and 10 days after operation but may occur as late as 3 weeks afterward In most instances the bleeding is internal, the blood passing down the ureter from the pelvis and thence into the bladder, but occasionally, as in a case in our series, fresh and clotted blood makes its exit through the wound in the flank Blood loss is frequently massive and shock is likely to be severe Pain is also severe in most cases because of the obstruction of the ureter by blood clots

The pathogenesis of secondary hemorrhage after nephrolithotomy is explained by infarction of the renal parenchyma, which may or may not be associated with infection The chain of events is clear With every incision into the renal cortex, many small terminal vessels are severed Also, as in every wound, there is a thin layer of necrotic tissue in the wound edges This area of necrosis is increased by what Joly calls "defective" suture of the wound The mattress type of suture, in which strangulation of tissue is frequent, was used in all 7 cases of secondary hemorrhage in our series

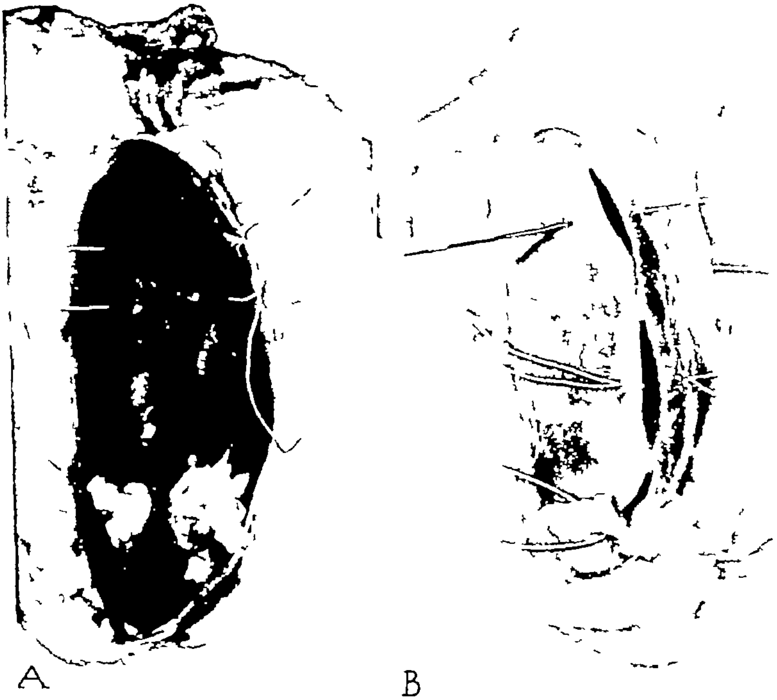

FIG 1 *A*, closure of nephrotomy wound after nephrolithotomy by mattress suture Note considerable amount of renal parenchyma included in suture, which introduces sequence of strangulation of tissue infarction, and secondary hemorrhage *B* technique of nephrotomy closure after nephrolithotomy by approximation of edges with double chromic No 1 suture, tied over pieces of fat Technique eliminates risk of strangulation of tissue and infarction inherent in closure by mattress sutures

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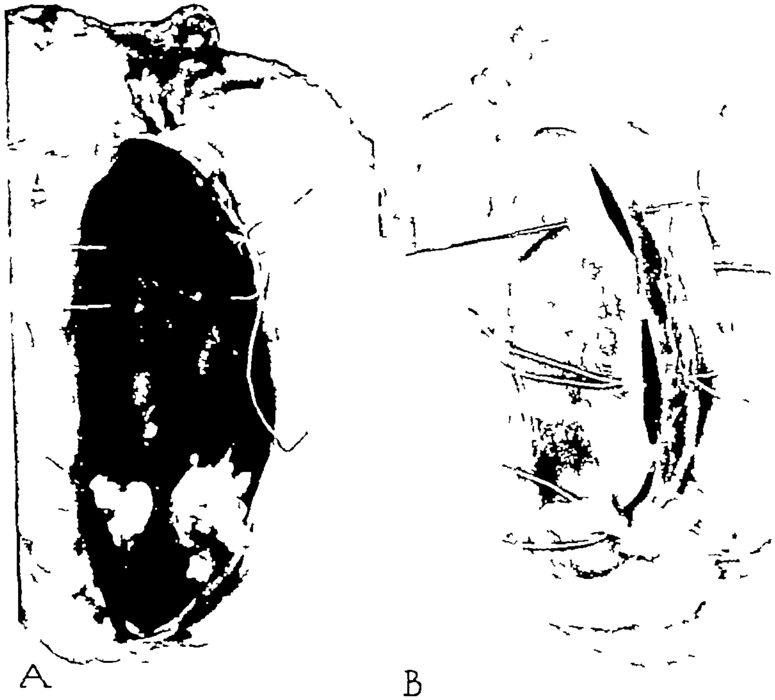

FIG 1 A, closure of nephrotomy wound after nephrolithotomy by mattress suture Note considerable amount of renal parenchyma included in suture, which introduces sequence of strangulation of tissue infarction, and secondary hemorrhage *B*, technique of nephrotomy closure after nephrolithotomy by approximation of edges with double chromic No 1 suture, tied over pieces of fat Technique eliminates risk of strangulation of tissue and infarction inherent in closure by mattress sutures

Joly places great emphasis upon infection as a contributory factor in secondary hemorrhage This seems a reasonable point of view It is entirely conceivable that infection would delay natural healing processes and would increase the sloughing, necrotic zone of tissue always present in the edges of the wound

In one case in our series an interesting contributory factor was the development of hypoprothrombinemia This patient had received terramycin for several days before and after surgery, and it was assumed that vitamin K formation had been inhibited because of sterilization of the lower bowel The bleeding ceased as soon as the antibiotic was discontinued and vitamin K was prescribed

CLOSURE OF THE RENAL PARENCHYMA BY AN IMPROVED TECHNIQUE

The review of these 75 cases and, in particular, the analysis of the 7 cases of secondary hemorrhage, led us to change our technique of closure of the renal parenchyma This technique, to our knowledge, has not previously been described It has been used during the past year in 15 cases, which are not included in the 75 cases analyzed and in which, it would seem on the basis of the previous experience, one or more cases of secondary hemorrhage might otherwise have been expected Instead, recovery in all of these cases was smooth and uncomplicated

The renal parenchyma was closed in most cases in this series of 75 cases, and in all 7 cases of secondary hemorrhage, by mattress sutures (fig 1, *A*) Obviously, this type of suture results in strangulation of tissue, with increase in the area of necrosis present in all wounds, and thus increases the chances of secondary hemorrhage

The technique which we have used for the past year in our opinion eliminates this risk The calyx is first closed with interrupted sutures of 000 catgut All

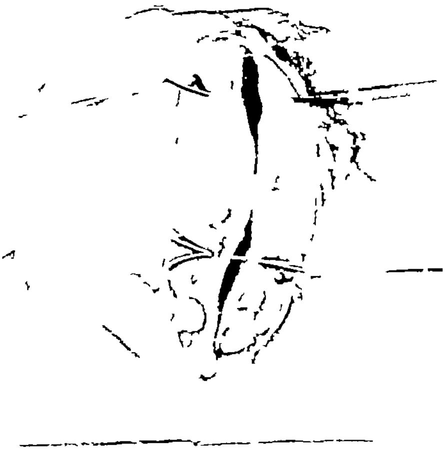

FIG 2 Technique of nephrotomy closure after nephrolithotomy shown in figure 1 *B* with utilization of Dees's renal needles instead of the Keith needle

large vessels are tied separately The wound in the cortex is then approximated by interrupted double sutures of chromic No 1 catgut, tied over pieces of fat and muscle on each side of the wound (fig 1 *B*) A large, curved, cutting needle or a straight Keith needle (fig 2) can be used, but our own preference is for the crochet type of needle designed by Dee (fig 2), the use of which greatly simplifies closure

Neither strangulation nor constriction of renal tissue has been observed in any of the 15 cases in which we have used this technique during the past year, and hemostasis has invariably been satisfactory

Nephrostomy is employed after nephrolithotomy only when it is clearly indicated In our opinion, it is an additional invitation to necrosis and infection of the parenchymal tissue If drainage is necessary for as long as 2 or 3 weeks, we prefer, if it is at all possible, to institute it through a straight rubber catheter placed directly into an opening in the pelvis rather than into the renal cortex In our experience, the results of drainage by pyelostomy have always been satisfactory

SUMMARY

Secondary hemorrhage and persistent urinary fistula are the most frequent complications of nephrolithotomy The reported incidence is close to 10 per cent and nephrectomy is necessary to control the bleeding in half or more of all cases An analysis of a personally collected series of 75 cases leads to the same conclusions

Secondary hemorrhage is presumably the result of necrosis and infarction of the renal parenchyma, which, it is reasonable to assume, are attributable, in many cases, to the use of mattress sutures for closure of the parenchymal wound A technique of closure is described in which these risks are eliminated and which has been used successfully in 15 cases during the past year

The most frequent cause of persistent urinary fistula is the performance of a conservative operation on a grossly diseased kidney, for which nephrectomy is indicated An overlooked obstruction of the ureter is another frequent cause

Because of its serious consequences, nephrolithotomy should not be performed unless there are definite contraindications to management of the case by pyelolithotomy

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MEDIAL RENAL PTOSIS

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Medial renal ptosis designates a syndrome by which the kidney may migrate from its normal fossa, across the midline. It is not associated with nor should it be confused with caudal ptosis. Associated with this abnormal renal movement is upper quadrant discomfort, varying in intensity of pain from mild to severe and having tendency to radiate downward.

To my knowledge, two such cases have been previously reported, both by George Prather, who suggested the term of medial renal ptosis. The case I am presenting is that of a woman, aged 43, well developed, and above average in stature. She complained of having nagging pains in the upper right quadrant for 15 years. This pain would radiate downward to right flank and thigh. She stated that quite often she would have nausea and a feeling of something "jumping around" in her abdomen. The patient stated that she experienced acute and severe pain at times on assuming an upright position after leaning over. She stated that she could feel a mass in her upper right abdomen which she could, at times, push over to the opposite side.

On physical examination, a mass that could be moved medially was felt in the upper right abdomen, and was believed to be the kidney.

Cystoscopy and the usual retrograde pyelograms were done, the films being taken in the supine (fig. 1, *A*) and upright (fig. 1, *B*) positions. The pyelographic studies revealed both kidneys normally placed, good calyceal filling, and only minimal descent on the upright film. These findings caused some doubt as to whether or not the mass that was palpable was really the kidney.

A series of gastrointestinal studies were done and reported as normal.

The patient was requested to return to my office. On cystoscopy, catheters were passed to each renal pelvis. The patient was then requested to assume a half-sitting and forward position, and asked to maneuver this mass medially, holding it with her right hand. This being accomplished, x-ray studies were made with catheters in place (fig. 2, *A*) and also a right pyelogram (fig. 2, *B*).

The films taken at this time yielded different information than the ones taken by conventional methods. The right kidney was clearly visualized overlapping the left kidney. As soon as the kidney was released it jumped back to its normal position.

Surgical exploration revealed the kidney lying in its normal fossa. On the medial side a wide defect in its fascial and paracapsular covering permitted the kidney to be easily pushed medially across the midline. This defect was closed and nephropexy was performed with excellent clinical and anatomical results.

I do not believe that medial renal ptosis is a common entity. However, the diagnosis will be difficult to make unless cases under suspicion are examined

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Read at annual meeting, Southeastern Section of American Urological Association, Hollywood Beach, Fla., March 25–29, 1956.

FIG 1 A, retrograde pyelogram, supine position B, retrograde pyelogram, upright position

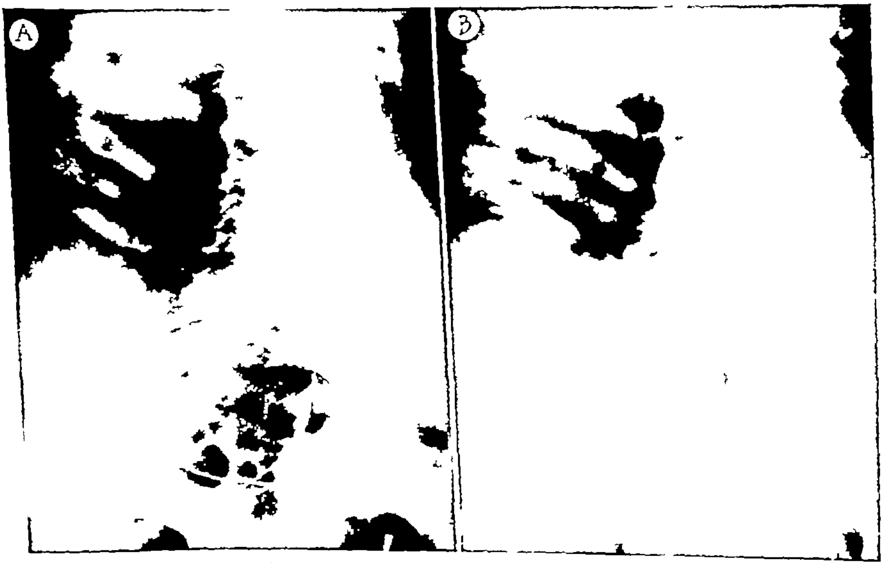

FIG 2 A X ray with catheters in place and patient holding kidney medially with right hand B right pyelogram with patient holding kidney medially with right hand

specifically for this condition This can best be done after cystoscopy and, before removing catheters, by having patient placed on regular x-ray table in lateral decubitus position with affected or painful side up, making retrograde pyelograms and taking an anteroposterior view

SUMMARY

A case has been presented that demonstrates medial mobility of the kidney, giving rise to symptoms not associated with other pathological changes

The term, medial renal ptosis, I believe, is applicable and suited to this syndrome

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RENAL FUNCTION IN DOGS FOLLOWING TRANSPLANTATION OF THE URETERS TO AN ISOLATED SIGMOID POUCH

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Hyperchloremic acidosis following transplantation of the ureters into the colon is a well defined clinical entity The pathogenesis of the plasma hyperchloremia has been extensively studied and ascribed to various factors predisposing to renal dysfunction,[1] [2] [3] Reflux of colonic urine and bacteria to the urinary pelvis secondary to elevated intracolonic pressure has been reported to underly the recurrent episodes of ascending pyelonephritis in some patients with ureterosigmoidostomy Hydronephrosis resulting from partial obstruction secondary to ureteral stricture in the region of the anastomosis is also significant in compromising renal function and in predisposing to renal infection The pathological alterations in the kidney resulting from hydronephrosis and pylonephritis result in a progressive decrease in glomerular filtration rate and renal blood flow [4] [5] In the patients whose renal blood flow and glomerular filtration are severly compromised, there is decreased renal excretion of phosphate and chloride and the acidosis is enhanced by impaired tubular exchange of ammonia and titratable acid for sodium [6]

A nipple type of ureterointestinal anastomosis has previously been reported[7] with the dual purpose of preventing the reflux of bacterial contents from bowel to renal pelvis and of decreasing the incidence of stricture formation at the ureterocolonic junction Use of this anastomosis in conjunction with an isolated sigmoid pouch obtained through use of a diverting colostomy provided the experimental preparation employed

The experiments reported here were carried out on dogs to study renal alterations and bowel absorption following this type of ureterointestinal anastomosis, either into an isolated sigmoid pouch or into the intact colon None of the animals

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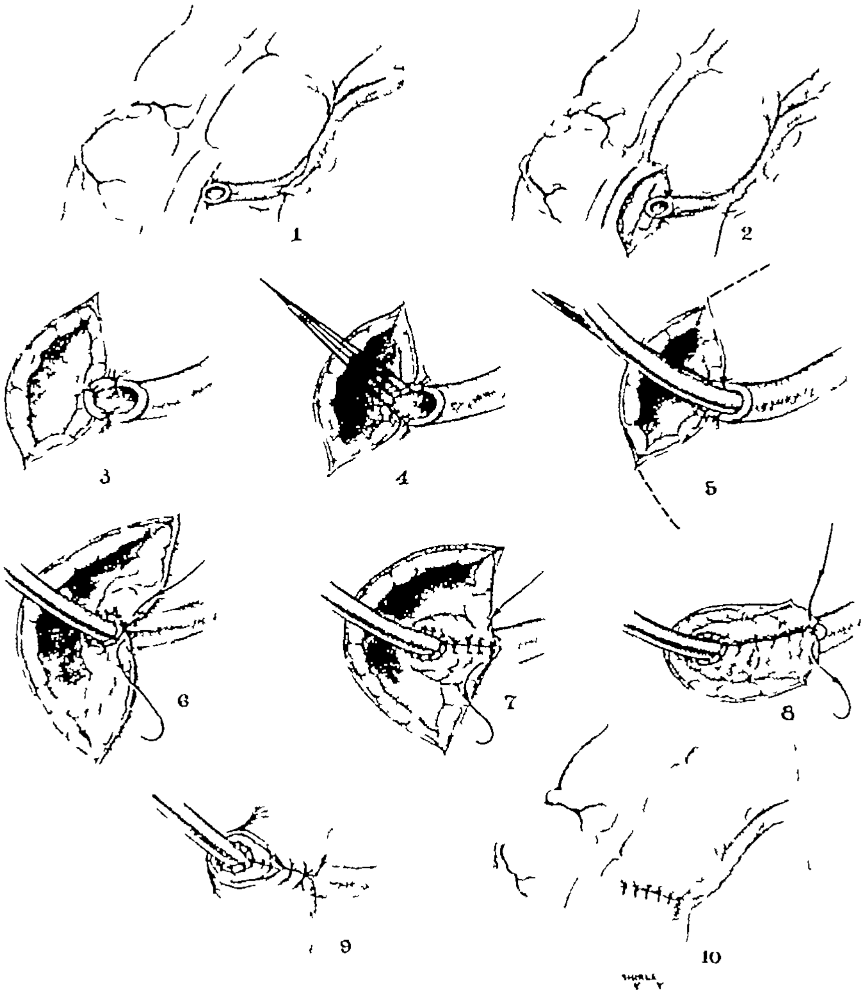

FIG 1 Surgical technique utilized in performing the ureterointestinal anastomosis (See text)

with the anastomosis of the ureters to the sigmoid pouch as described here developed hydronephrosis or pyelonephritis, and the pouch remained free of bacterial infection

METHODS

Surgical technique The main principle in transplanting the ureters to the bowel is to form a bowel nipple for the opening of the ureter The technique for transplantation is the same as previously reported[8] with the following modifications illustrated in figure 1

The ureters are exposed through a midline incision and cut close to the bladder To ensure an adequate blood supply to the end of the ureter we have used a flourescein* test, i e 5 cc flourescein solution is injected intravenously and the end of the ureter is observed under a quartz lamp If the ureter fluoresces, a sufficient blood supply is assured

The end of the ureter is incised on its posterior lip and anchored transversely to the long axis of the sigmoid, but longitudinally to the axis of the bowel flap, using fine silk sutures passing through the outer layer of the ureter, one at the apex and one at the base of the bowel flap The bowel is incised longitudinally at the tip of the ureter down to the mucosa for a distance corresponding to the circumference of the ureteral stoma The musculature is dissected from the mucosa, laterally, for a width of 1 cm by means of mosquito forceps The bowel mucosa is then incised The posterior portion of the free end of the ureter is sutured to the bowel mucosa using 5-0 silk on an atraumatic needle At this stage a fine rubber catheter is passed up the ureter A bowel flap is made by incising the muscularis and the mucosa of the bowel at each side of the ureter for a length of 2 cm The anterior circumference of the free end of the ureter, i e the anterior part, is now sutured to the bowel mucosa The sides of the bowel flap are then brought together in front of the ureter using interrupted fine silk sutures which should include the outer layer of the ureter A nipple or papilla is thereby formed which projects into the lumen of the bowel The remaining opening in the bowel is closed in two layers by interrupted sutures, the second layer of sutures is started at the base of the flap and the catheter is left in to prevent constriction of the ureter until the initial sutures have been placed The catheter is then removed and the remaining opening in the bowel is closed in two layers The bowel is anchored firmly at the site of anastomosis to prevent any tension on the anastomosis or kinking of the ureter

In our experimental studies we used 12 mongrel dogs weighing between 10–20 kilograms In one group, the ureters were transplanted to a sigmoid pouch bladder and a proximal colostomy was performed In another group, only one ureter was transplanted to the bowel leaving the opposite ureter and kidney intact After the operation the dogs were kept in the kennel three to seven months before any experiments were performed

Procedure In the animals with unilateral ureteral transplants, renal function and colonic absorption were studied in the kidney with the ureter transplanted to the bowel In the animals with both ureters transplanted to the colon, renal function was studied in both kidneys simultaneously The renal function studies reported here included measurements of inulin and para-aminohippurate clearance and excretion of ammonia, chloride, sodium and potassium Prior to the beginning of the experiment, indwelling catheters were inserted into the rectum and into the bladder for the collection of urine Electrolyte excretion was then measured a) during a control interval in which urine was draining freely through

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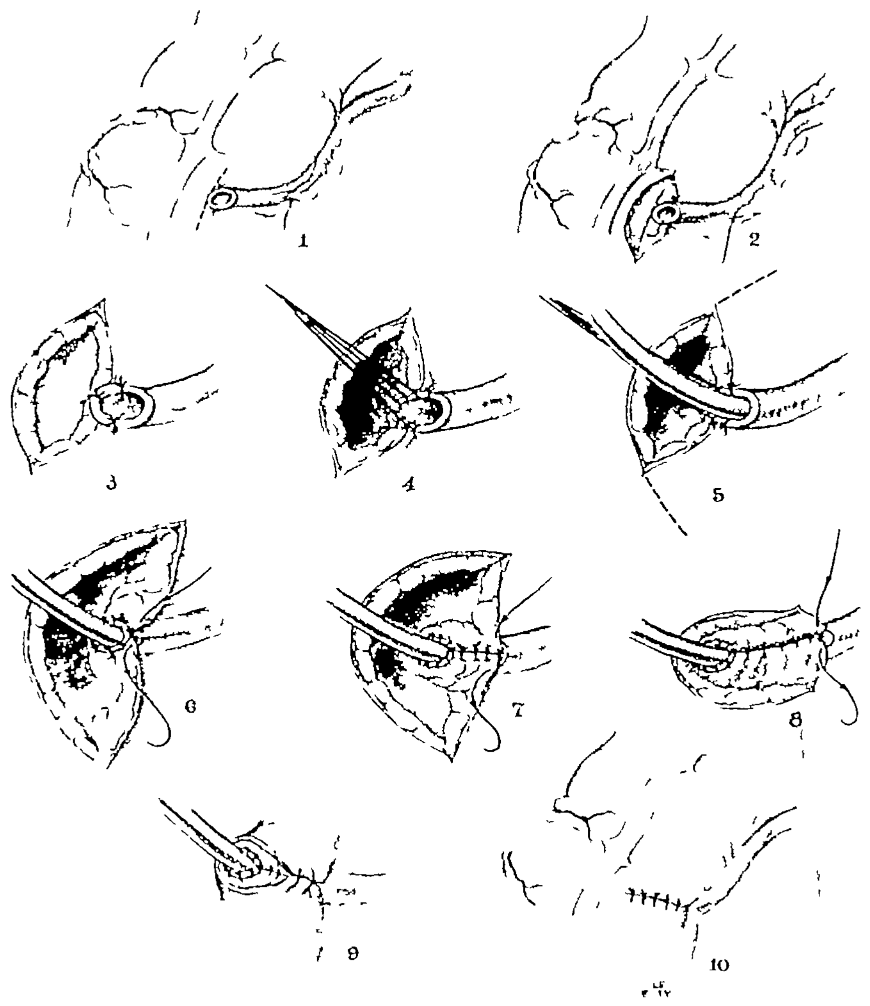

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The absorption of ammonia from the colon was measured by placing a polyethylene catheter or an indwelling needle in 1) a peripheral artery, 2) the superior mesenteric vein, and 3) the sigmoid vein Simultaneous samples of bloods drawn from these three sites and samples of urine from the colon or bladder were analysed for their content of urea, ammonia, chloride, pH, and phosphate In four experiments, urine was secured from a pyelotomy performed on the kidney with its ureter transplanted and the chemical analysis of this urine compared to that of urine obtained from the colon

Chemical analysis and methods for obtaining the samples of blood and urine were carried out according to methods previously described [8] Urine was collected, the pH done immediately and the specimen then stored with a preservative for subsequent analysis

TABLE 1 *Alterations in electrolyte excretion resulting from storage of urine in colon*

	Inulin Clearance cc/min	Para Amino Hippurate Clearance cc/min	Urinary Excretion		
			Potassium	Chloride	Sodium
				μEq/min	
Dog 40 One ureter in sigmoid pouch					
a) Control	22	79	27	52	24
b) Catheter clamped Urine retained in sigmoid 120 mins	14	43	18	12	32
Dog 136 One ureter in intact colon					
a) Control	48 7	128	33	179	15 8
b) Catheter clamped Urine retained 60 mins	33	74	25	53	77
Dog 105 One ureter in sigmoid pouch					
a) Control	43	150	27	228	—
b) Catheter clamped Urine retained 60 mins	20	96	36	16	—
Dog 89 Both ureters in sigmoid pouch					
a) Control	93	221	11	42	16
b) Catheter clamped Urine retained 120 mins	21	78	29	9	70
Dog 95 One ureter in sigmoid pouch					
a) Control	20	72	30	30	210
b) Catheter clamped Urine retained 120 mins	19	51	29	7	252

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[8] Roberts K L and Pitts R F The influence of cortisone on renal function and electrolyte excretion in the adrenalectomized dog Endocrinology 50 51, 1952

TABLE 2 *Comparison of ammonia content in sigmoid vein superior mesenteric vein and urine previous to and following storage of urine in intact colon and sigmoid pouch*

Time (min.)	Urine Ammonia mEq/L		Blood Ammonia µEq/L	Urine pH	
	Pelvic Urine	Sigmoid Urine	Sigmoid Vein	Pelvic Urine	Sigmoid Urine
Dog 136 Ureter in sigmoid—colon intact					
Control	22	14	85	6.0	6.0
Urine retained in colon					
120	33	122	785	6.6	8.0
Dog 120 Ureter in sigmoid pouch—proximal colostomy					
Control	4.4	8.1	227	6.5	5.2
Urine retained in sigmoid					
120	2.2	6.3	243	4.8	5.0

RESULTS

Alterations following elevation of intracolonic pressure. The alterations caused by storage of urine in the sigmoid are illustrated in table 1, which shows para-aminohippurate and inulin clearances and electrolyte excretion a) during a control interval when urine was draining freely from the rectal catheter and b) during an interval when the catheter was clamped and urine was allowed to collect in the colon. The clamping of the catheter resulted in elevation of intracolonic pressure to as high as 35 cm. of water and as shown here, there was a decrease in renal clearances and a decreased excretion of chloride. These were consistent findings following retention of urine in the colon and elevation of intracolonic pressure regardless of whether the ureter was transplanted to the sigmoid pouch or the intact colon. The significance of the decreased clearances of para-aminohippurate and inulin cannot be clearly ascribed to changes in renal blood flow or glomerular filtration since these substances are also absorbed across the bowel mucosa if allowed to remain in the bowel for a period of time. It is likely, however, that the decrease clearances of these substances are not entirely due to bowel absorption, but probably represent a decrease in renal function as well. These studies do not indicate whether the decreased chloride concentration represents a decrease in renal filtration of chloride or whether it is due to bowel absorption.

The absorption of ammonia from the colonic urine was studied by comparing the concentration of these constituents in the urine and in venous drainage from 1) a sigmoid vein, 2) the superior mesenteric vein, and 3) the femoral artery, simultaneously. These determinations were done during a period when urine was draining freely from the indwelling rectal catheter and during intervals of 60–120 minutes when the catheter was clamped and urine retained either in the isolated sigmoid pouch or in the intact colon

Table 2 shows the marked difference in the ammonia content of sigmoid vein blood and urine in one animal with retention of urine in the intact colon and in one animal with retention of urine in the sigmoid pouch As shown in these experiments, there was no significant elevation of blood ammonia in either animal when the urine was draining continuously from the rectal catheter In the dogs whose ureters had been transplanted to the intact colon, however, there was a marked elevation of ammonia both in the sigmoid vein and in the colonic urine when the rectal catheter was clamped and urine allowed to remain in the intact colon for 120 minutes This was a consistent finding in all of the animals with ureters transplanted to the intact colon

Similar measurements of ammonia content of urine retained in the sigmoid pouch and in venous drainage from the pouch are also summarized in table 2 As illustrated, there was no elevation in ammonia content of sigmoid vein blood or in the urine from the sigmoid pouch even when the urine was retained in the sigmoid for periods up to two hours No change in chloride concentration in sigmoid vein blood was measured either previous to or following retention of urine in the sigmoid pouch or the intact colon

In four experiments, measurements of ammonia in urine obtained from the renal pelvis were compared to those obtained from the intact colon A significant difference in ammonia concentration of pelvic urine and colonic urine was not measured when urine was draining freely from a rectal catheter The concentration of ammonia in colonic urine exceeded that of pelvic urine, only with storage of the urine in the intact colon for periods of 60–120 minutes

Pathological examination, intravenous pyelograms and direct observation failed to reveal any renal damage, pyelonephritis or hydronephrosis in the dogs studied by us during the interval ranging between 7-12 months following transplantation of the ureters to the sigmoid bladder by the technique herein described

Blood electrolytes remained within normal limits in all animals whose ureters were transplanted to the sigmoid pouch One animal whose ureters had been transplanted to the intact colon developed hyperchloremic acidosis and hypokalemia

SUMMARY AND CONCLUSIONS

The type of anastomosis into an isolated sigmoid segment as described here would appear to offer the following advantage the sigmoid pouch is sterile and should, therefore, decrease the chances of ascending pyelonephritis and 2) reflux of contaminated colonic urine to the renal pelvis is prevented It does not, however, prevent the decreased excretion of chloride when urine is stored in the pouch In this respect it is probable that a urinary pouch which is continuously drained would offer a greater advantage Although a sigmoid segment has been used in these studies for transplantation of the ureter, other segments of lower bowel serve equally well for this purpose[4, 5, 6] This is supported by the finding of Perry et al[8] that human subjects with ureters transplanted to a sigmoid or ileal segment may maintain normal renal function and that the urine of these patients remained sterile Bricker[9] has also reported that patients with isolated ileal pouches do not develop hyperchloremia

Our observations confirm the reports of elevated ammonia content in sigmoid vein blood due to colonic absorption of ammonia[10, 11] In our experiments we presume this was due to bacterial decomposition of urea in the intact colon since a similar elevation of ammonia has been described in inferior mesenteric vein blood in normal dogs and is not peculiar to the situation of ureterointestinal anastomosis[12] The finding that ammonia was not elevated in the sigmoid vein or in the urine of animals with ureters transplanted to the isolated sigmoid pouch merely reflects that the pouch was bacteriologically sterile

[9] Bricker Eugene Bladder substitution after pelvic evisceration Surg Clin N Am, 30 1511 1950

[10] Boyce W H and Vest S A Role of ammonia reabsorption in acid-base imbalance following ureterosigmoidostomy J Urol 67 169 1952

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VESICORECTOSTOMY

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Diversion of the urinary stream in cases of lower tract disease is not a new idea Diversion to the skin has been practiced since the year 1556, when Pierre Franco reported the first suprapubic cystotomy Deliberate creation of a fistula between the urinary tract and the intestinal tract is thus a relatively new procedure, having first been done in 1896 Ureterosigmoidostomy has not only permitted curative surgery for many formerly incurable bladder lesions, but has given many more inoperable persons palliation from intractable pain of bladder malignancies, contracted bladder and so forth However, even utilizing the newer techniques of submucosal tunneling and direct mucosa-to-mucosa anastomosis, the procedure has a definite and considerable mortality, and with certain postoperative complications Leadbetter and Clark reviewed 2897 reported cases and found a mortality rate of 15 5 per cent of 780 cases where all types of anastomosis were used, and cystectomy was not done They also reported normal postoperative pyelograms in only 67 per cent of 41 cases operated on by the combined tunnel and direct anastomosis We have seen a number of patients with lesions distal to the bladder who would benefit by diversion of the urinary stream, but the immediate and delayed hazards of ureterosigmoidostomy caused us to hesitate Therefore, it was with extreme interest that we read the report of 2 cases of J G Moore of Pittsburgh, in which he made an artificial communication between the bladder floor and the rectum The name, vesicorectostomy seems descriptive and well suited for the procedure

Vesicorectostomy may be indicated in any obstructing lesion distal to the vesical neck which fails to respond to the usual method of treatment Patients with inflammatory, congenital or traumatic urethral strictures in whom resection or dilatation fails to produce the desired results are suitable candidates, as are those with urethroperineal, urethroscrotal or urethrorectal fistulas Obstructing prostatic malignancies may be by-passed by this method and the patient made symptom-free for a time Destructive lesions of the urethra which would require permanent cystostomy may thus gain relief without the burden or complications of catheter life, and without any increase in operative mortality over that of cystostomy It may also prove valuable in bladder lesions resulting in severe contracture such as interstitial cystitis or old healed tuberculosis

It is perhaps superfluous to mention that rectal continence is an absolute prerequisite for consideration of this operation, and this fact limits its usefulness in neurogenic bladder disease

Preoperatively the patient is given castor oil and a liquid diet followed by neomycin and sulfathaladine for 2 days in order to sterilize the bowel This is

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Read at annual meeting, Southeastern Section of American Urological Association, Hollywood Beach Fla March 25–29, 1956

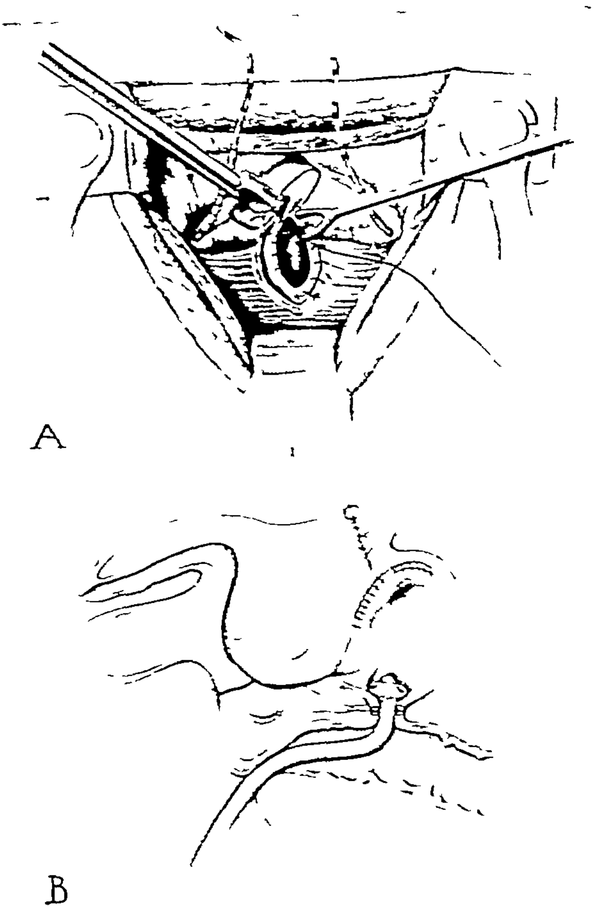

FIG 1 A showing approximation of bladder to bowel mucosa Note sigmoidoscope appearing in wound B sagittal section of completed anastomosis showing catheter in place

especially important since we have done all cases in one stage without preliminary suturing or injection of sclerosing agents into the cul de sac area and the possibility exists of entering the peritoneal cavity during the process of creating the fistula The patient is placed supine on the table with his thighs slightly abducted to facilitate introduction of a sigmoidoscope which is passed into the rectum (fig 1 A) The bladder is widely opened through a midline suprapubic incision and the trigone exposed Ureteral catheters are passed up each ureter and left in place to prevent accidental suturing of the ureter during the anastomosis An assistant then grasps the sigmoidoscope under the drapes and forces the beak upward firmly against the bladder floor in the midline An incision is made beginning at the interureteric ridge and continued up the posterior bladder wall for 3 cm This incision is carried through the bladder and rectal walls to expose the rectal instrument The presence of the sigmoidoscope greatly facilitates this stage of the procedure by giving support to the rectal wall against the knife blade

After the fistula has been determined to be of adequate size, or approximately 3 cm , the rectal mucosa is grasped and the boomerang needle passed from the rectal side through the bladder Each side of the anastomosis is made with a separate, continuous, chromic catgut suture, and the mucosa of the bladder is approximated to that of the rectum as closely as possible Use of the boomerang needle and Harris threader is strongly recommended for this phase of the procedure because the incision is of limited size and, particularly in the obese individual, lies deep within the pelvis (fig 1, *B*) A 36F de Pezzer catheter is passed into the rectum through the fistula, drawn down by the assistant and allowed to remain indwelling Prior to closing the bladder wall anteriorly an inspection will reveal whether it is of advantage to resect part of the bladder to reduce the capacity Following this the wound is closed tightly without drains, and the catheter connected to constant drainage for about a week, after which it is removed In the delayed postoperative period the fistula should be periodically dilated for several months In three of our four cases it has been possible to easily slip the index finger into the bladder through the rectum

CASE REPORTS

Following is an account of our experience with this procedure

Case 1 C D , a 65-year-old Negro, underwent a total prostatectomy for cancer in January 1953, with accidental laceration of rectum, subsequent rectourethral fistula and severe stricture of the membranous urethra distal to the fistula He was first seen by us 2 months postoperatively and complained of difficult and painful voiding, passage of feces per urethram and leakage of urine from the rectum In March 1953, a sigmoid colostomy was performed and a urethral catheter was left indwelling for the next 3 months, but was removed because of difficulty of repeated obstruction from mucus and feces He continued to void partly from the rectum and partly from the urethra and suffered increasing bladder spasm and hematuria In December 1954, the patient complained of weight loss, weakness, urgency, frequency 5 times an hour and intermittent suprapubic pain On December 10, 1954, a vesical lithotomy and enlargement on the trigone of the existing vesical fistula were performed The catheter was removed on the seventh postoperative day Excretory urography 1 year postoperatively (December 1955) was normal The patient had gained strength and weight and was generally improved

Case 2 C C , a 22-year-old white man, sustained a fractured pelvis and a lacerated urethra in 1943, at which time he was treated only by catheter drainage He subsequently had repeated episodes of urinary retention due to a urethral stricture and underwent 8 operative procedures, i e , urethroplasties and cystostomies The last plastic procedure was done July 16, 1954 It was unsuccessful and the cystostomy was left in place He exhibited considerable bladder symptoms and was found to have a vesical calculus He was hospitalized and on December 13, 1954, vesicolithotomy and vesicorectostomy were performed At the time of surgery marked scarring about the bladder base and posterior bladder wall was noted The procedure and postoperative course were entirely uneventful and on the seventh postoperative day the catheter was removed Postoperatively we were unable to palpate the fistula digitally, and repeated sigmoidoscopies failed to visualize the fistula However, pyelograms demonstrated the bladder to be emptying satisfactorily, and he has remained asymptomatic

Case 3 O M, a 44-year-old Negro, underwent suprapubic cystotomy in March 1948 for long standing urethral strictures with repeated abscesses and subsequent urethroperineal and urethroscrotal fistulas He had worn a cystotomy tube for 7 years, he had been seen in the outpatient clinic and had his tube changed 148 times He complained of severe debilitating bladder spasms and had thick syrupy urine Excretory urography showed an intact upper tract, and a contracted bladder containing two stones On January 7, 1955, vesical lithotomy and vesicorectostomy were performed The peritoneal cavity was inadvertently entered through the incision in the posterior bladder wall requiring the use of a pack to keep small bowel from entering the field The anterior half of the bladder wall was resected His postoperative course was marked by a protracted paralytic ileus undoubtedly due to gross contamination of the peritoneal cavity by the infected bladder contents On his eighteenth postoperative day the catheter was removed and he has been without complaint since Excretory urography 1 week postoperatively showed moderate right hydronephrosis This may be explained by the fact that no urethral catheters were used, and one wall of the ureter may have been caught by a suture

Case 4 J S, a 57-year-old Negro, had lower urinary tract infection, intermittent right renal pain, constant low back ache, dysuria and multiple nocturia associated with urethral strictures for 9 years In February 1947, a transurethral resection of a fibrous prostate was done He continued to receive periodic dilatation In March 1949, a periurethral abscess resulted in multiple urethroperineal fistulas and these were resected His stricture and infection persisted and he received dilatations until 1953, when his fistula again opened In October 1954, incision and drainage of a periurethral abscess were done In November 1954, the patient again noted urine leaking from the anal sphincter area at the time of voiding In January 1955, the patient again noted urine leaking from the anus although his urethra tolerated a No 22 sound He also complained of constant severe rectal pain, moderate right flank pain, and weight loss of 30 pounds over a 6-month period Preoperative pyelograms were compatible with chronic pyelonephritis On June 6, 1955, an uneventful vesicorectostomy was done He did well for 2 days, then had a sudden bladder hemorrhage The bladder was opened and the clots evacuated, but attempts to find the active bleeding point were unsuccessful The catheter was removed on the seventh postoperative day A tiny suprapubic fistula persisted for six more days, then healed completely He remained asymptomatic, gained weight and worked regularly except for one episode of fever, chills right flank pain and hematuria 5 months after surgery Pyelograms at this time showed no change in appearance from the preoperative films

Vesicorectostomy is not designed to replace any present procedures, but rather to supplant them in certain instances where disease is limited to the lower urinary tract One major advantage offered by this procedure is that the important valve action of the ureterovesical junction is preserved This should materially reduce the incidence of postoperative pyelonephritis and hydronephrosis It would also seem that the operative mortality should not exceed that of suprapubic cystotomy and certainly the postoperative complications of infection, stone, and bladder spasm have not been seen thus far The problem of reflux of feces through the fistula and into the bladder during defecation remains A barium enema done in the postoperative period on one patient showed the bladder well filled with the solution The post-evacuation films, however, demonstrated the bladder to be empty Whether or not this is of significance in the development of pyelonephritis has not been determined However, except in one instance, acute pyelonephritis has not occurred in these patients to date, and one would think that the constant stream of urine through the fistula into the rectum would keep the bladder free of debris Also, whether reduction of bladder capacity by resection is of real or only apparent benefit cannot yet be ascertained We have been favorably impressed by the early results of this procedure All of the patients have tolerated the operation very well, the postoperative course has been remarkably smooth and free from side effects There has been no significant change in chemistries, and the alleviation of symptoms in all cases has been dramatic In conclusion we believe that when the proper indications are observed, vesicorectostomy will prove a valuable adjunct in the management of difficult cases of lower urinary tract dysfunction

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ORCHIDOFUNICOLYSIS

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The word, orchidofunicolysis is a comparatively new term, at least in the medical literature of this country, and has not yet reached our medical dictionaries It is applied to an equally new operative technique for treatment of all types of undescended testes, and takes its name from three medical words in current use, viz , orchio (L *orchis*) meaning testis, funicle (L *funiculus*) a slender cord, usually the spermatic cord, and lysis, signifying dissolving or detachment [1]

The term, orchidofunicolysis and the operative procedure that it represents were first introduced to the medical profession of this country by Beltrame[2] in January 1954 The report was based on the earlier work of Guiliani, surgeon of S Martino Hospital in Genoa [3] Certain features of the operation, notably the lysis of all adhesions, and thorough mobilization of the structures involved, have been described by other surgeons, especially Keetley,[4] Bevan,[5] Torek[6] and Ombrédanne [7] Beltrame, however, stresses the importance of a direct pathway to the scrotum This objective is obtained by painstaking orchidofunicolysis, and the elimination of lateral excursion along the way More recently Prentiss et al [8] have contributed materially to this phase of the subject

Torek in 1931[9] attempted to put an end to the confusion which existed concerning the terms, orchiopexy, orchidopexy and orcheopexy which are applied to the operation for undescended testicle If the profession were to accept Torek's classical description of the Greek origin of these terms, the prefixes, orcheo and orchio would be declared etymologically correct, and orchido would be dropped from the literature It would then follow that the operation herein described would be known as orcheofunicolysis Practically speaking, this operation is a form of orcheopexy, except that such a term is less descriptive

HISTORICAL DATA

According to Cabot and Nesbit,[10] the earliest recorded orcheopexy was described by Rosenmerkel in 1820 It consisted merely of fixation of the testis to

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Read at annual meeting, Southeastern Section of American Urological Association, Hollywood Beach Fla March 25-29 1956

[1] New Gould Medical Dictionary, first edition Philadelphia Blakiston, 1949

Beltrame E J Internat Coll Surg , 21 472-476, 1954

[3] Giuliani G M Nuovo metodo operatorio per la cura dell'ectopia sottocutanea inguinale addominale del testicolo Arch ital chir , 75 253-284, 1952 (Article is fully illustrated)

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[5] Bevan A D Operation of undescended testicle and congenital inguinal hernia J A M A 33 773 1899

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Ombrédanne L L'orchidopexie chez l'enfant Gaz méd de France 2 118-123, 1928

[8] Prentiss R J Mullenix R B and Whisenand, J M A M A Arch Surg 70 283-290, 1955

[9] Torek F Orchipexy for undescended testicle Ann Surg 94 97-110, 1931

[10] Cabot Hugh and Nesbit R M Undescended testis Arch Surg 22 850-856 1931

the fundus of the scrotum with a suture Max Schuller, in 1881,[11] was the first to handle the problem of undescended testicle logically Schuller devised the operation which Bevan later perfected,[12] and with few exceptions, as far as mobilization and lengthening of the cord structures are concerned, has persisted as the operation of choice until very recently Bevan maintained that it was not the shortness of the vas, but of the vessels, which prevents placing the testis in the scrotum Therefore, his principal contribution was the lengthening of the vessels by separating or cutting the adhesions between their loops, and by freeing them from the peritoneum He further recommended his pursestring suture of catgut in the superficial fascia, at the top of the scrotum This, according to Bevan, prevents the testicle from slipping back into the groin and keeps it well down in the scrotum While both of Bevan's procedures have had an influence[3] on the modern technique for the surgical correction of undescended testis, their individual value as a completely corrective procedure, each within itself, has been grossly overemphasized

The British surgeon, C B Keetley (1905)[4] preceded the American surgeon, Franz Torek of New York City (1909)[6] with a description of the operation, which had as its basic principle the temporary fastening of the testicle or its gubernaculum to the fascia lata of the thigh Torek, working independently of Keetley and, according to his original publication, with no knowledge of the Keetley operation, developed practically an identical surgical technique for the correction of cryptorchidism The Keetley operation later became known as the Keetley-Torek operation and finally, in this country at least, as the Torek operation This is an injustice, for Torek himself acknowledged that priority in the development of the operation for undescended testicle, which embraced the principle of fixation to the fascia lata of the thigh, belonged to Keetley Therefore, such procedures, which are today loosely referred to as the Torek operation should more correctly be defined as the Keetley operation or, if you will, the Keetley-Torek operation

The general subject of undescended testes has been presented adequately in recent literature by Campbell,[13] Barney and Suby,[14] and by many others No effort will be made in this paper to duplicate the very thorough work of these authors

BASIC PRINCIPLES

Fixation of the testicle in the scrotum, while exceedingly important, is not the most important feature of operative procedures for the correction of undescended testicle If the testicle, its cord structures, and its blood supply are not adequately and properly mobilized, sufficiently lengthened and redirected, the testicle will never reach the bottom of the scrotum Forceful fixation to the thigh, if indeed possible, will only result in unjustifiably painful tension, torsion, and poor anatomical results regardless of the weeks or months it is left so attached Conversely proper mobilization, lengthening and redirection will allow the testicle to be placed nicely in the bottom of the scrotum, and to remain there almost without fixation Some form of simple temporary fixation, however, is advisable to maintain the desired anatomical position, and to prevent retraction This should be maintained until such time as the organ may be expected to remain in proper position of its own accord a matter of a few days only

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[11] Schuller, M On inguinal testicle and its operative treatment by transplantation into scrotum Ann Anat & Surg , 3 89, 1881

[1] Bevan A D Undescended testes Surg Clinics of Chicago, 2 1101–1117, 1918

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[14] Barney J D and Suby H J Anomalies of Scrotum and Testicles In Lewis' Practice of Surgery editor in chief Walters Hagerstown Md 1954 vol 3 chapt 28

"Since compression and immobility apparently impair the development of the retained gland, free replacement of the testis, before puberty, into the scrotum its normal anatomic and physiologic environment with thermo-regulation of the dartos etc allows it to regain its normal size and function,' Beltrame[2] Probably this is best accomplished before the age of nine Campbell recommends[13] "In bilateral cryptorchism, steps to correct the condition should be begun by the age of three to four years In unilateral cryptorchism one may wait until six years of age" Even after puberty and including the third decade, the operation may save a gland capable of some endocrine production if not spermatogenesis Because of active interstitial cell development in these glands, orchiectomy should never be given consideration at any age[10]

MEDICAL TREATMENT

Before proceeding to a description of the new operation which we employ for correction of undescended testicle, brief reference will be made to what appears to be the present medical thinking on the subject 1) multiple examinations to exclude alternating cryptorchism ectopic testis, hypoplasia of the testis and cord, and probable concomitant hernia, 2) trial periods of chorionic gonadotropic therapy (antuitrin S or follutein), 3) testosterone propionate therapy in hypogenitalism, 4) delay of surgical intervention until a suitable age, 5) spontaneous descent, if it is to occur, is usually completed by the first year 6) normal descent before puberty subsequent descent is unlikely, 7) high incidence of atrophy in untreated undescended testicles, 8) malignant degeneration is a possibility 9) high incidence of associated hernia, indirect inguinal type usually, 10) epididymitis——torsion of the cord——strangulated hernia are possible complications, 11) preservation of fertility is *the* most important consideration 12) endocrine and psychic disturbances must be considered

The results of hormonal therapy have been disappointing Some authors report that they have never seen a testis appear as a result of gonadotropic therapy Also, that its principal use is to mollify the parents while temporizing and to aid genital growth, enlarge the local structures and improve blood supply, preliminary to surgical correction[8]

ANOMALIES OF DESCENT

Anomalies of descent fall into two groups 1) the testis is arrested at some point along the normal course of descent, *cryptorchism*, 2) the testicle migrates to some abnormal position, *ectopia* These terms are also loosely employed today The imperfectly descended testicles are also described as 1) abdominal (lumbar or pelvic) within the abdomen, but behind the peritoneum, usually lying in

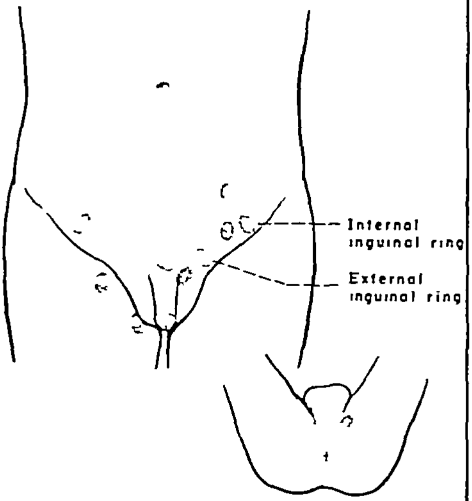


FIGURE 1

PERINEAL
ECTOPIA

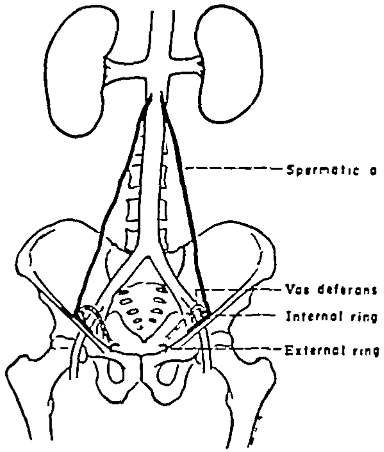


FIGURE 3

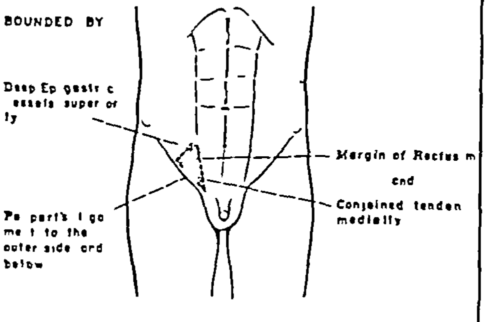


FIGURE 2

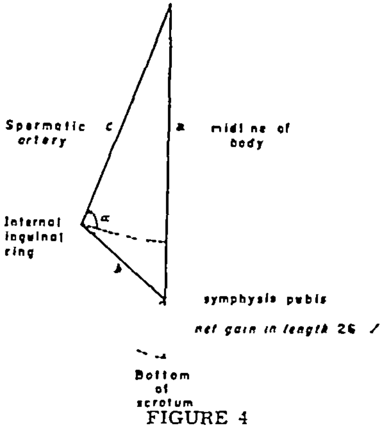


FIGURE 4

Fig 1 Types of undescended testicle (Adapted from Campbell Urology Philadelphia W B Saunders Co 1954, vol 1, fig 261)

Fig 2 Hesselbach's triangle

Fig 3 Juncture of spermatic vessel with vas deferens at internal inguinal ring

Fig 4 Dynamics of spermatic surgical triangle (Adapted from Prentiss, Mullenix and Whisenand A M A Arch Surg , 70 283–290 1955)

the lumbar or iliac regions, 2) subcutaneous, beneath the skin but outside the inguinal canal, overlying its roof or the external oblique fascia, 3) inguinal, lying in the inguinal canal, 4) subinguinal (prepubic or upper scrotal) at any point between the top of the scrotum, and the external inguinal ring (fig 1)

METHODS OF OPERATION

Over the years more than thirty different methods for the correction of undescended testicle have been devised Of these, few present sufficient variation in principle and procedure to deserve special mention As pointed out recently by Prentiss et al[6] When such multiplicity and variation of management of a medical problem occur none of the methods produces uniformly satisfactory results Certainly the 75-year-old operation of Schuller the 57-year-old improvement by Bevan the 51-year-old Keetley operation and its 47-year-old modification by Torek nor the 28-year-old Ombrédanne operation are, individually the final answer They have however individually contributed much to the gradual evolution of the more modern procedure

Once the surgeon has provided the desired length several methods for fixation are available They may briefly be described as follows

1) Operations in which the testicle is in some way attached to the fascia lata of the corresponding thigh——the Keetley-Torek operation (Perhaps no longer necessary considering the efficiency of the new procedure)

2) Operations wherein the testicle passes through the scrotal septum to the opposite side——the Ombredanne type[7] (Even less desirable)

3) Operations which embrace nonabsorbable sutures attached in some way to the testicle or its severed gubernaculum to be brought out through the bottom of the scrotum. and fastened to some anchoring agent preferably a stout adhesive band (fig 8) (Excellent and to be recommended as an adjunct to the new operation)

THE NEW OPERATION

Two anatomical triangles are important to this new procedure one is the well-known Hesselbach s triangle (fig 2) which is bounded by the deep epigastric artery superiorly Poupart s ligament to the outer side and below and the margin of the rectus muscle (conjoined tendon) medially The second triangle is new and is called the spermatic surgical triangle It is bounded medially by the midline of the body laterally by the abdominal course of the spermatic vessels and inferiorly by the inguinal course of the same vessels (figs 3 and 4)

The dynamics of this new spermatic surgical triangle (fig 4) are explained as follows The lateral deviation of the cord and vessels is eliminated by orchidofunicolysis and the tortuosity of the vessels involved is relieved This allows medial displacement The substitution of the more medial external inguinal ring for the more lateral internal ring as a pathway for the cord structures from the retroperitoneum to the scrotum takes advantage of the fact that a straight line is the shortest line between two points The relative increase in length through decreasing the distance to the scrotal pouch is 26 per cent (figs 4 and 5)

A second principle anticipates temporary fixation for the testicle in its new position For this purpose a wide (3-inch) adhesive preferably double thickness is securely wrapped around the mid-thigh on the side to be operated on so that its upper edge is on a level slightly below the lowest point of the scrotum (fig 8) This is applied preoperatively so that it may be included in the surgical preparation " which is otherwise as for herniorrhaphy Temporary fixation to this band makes the time-worn Torek fixation and its secondary operation unnecessary

Detailed description of the basic operative approach for undescended testicle has been adequately described elsewhere[2-4, 6, 12] and therefore needs no further repetition by me It will suffice to simply epitomize

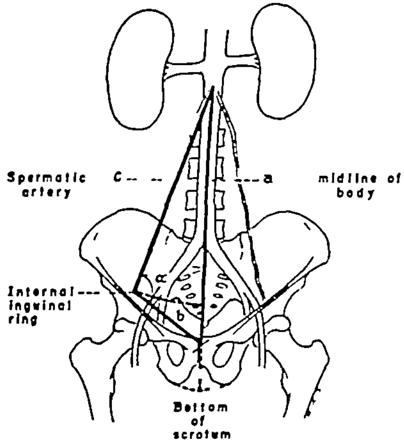
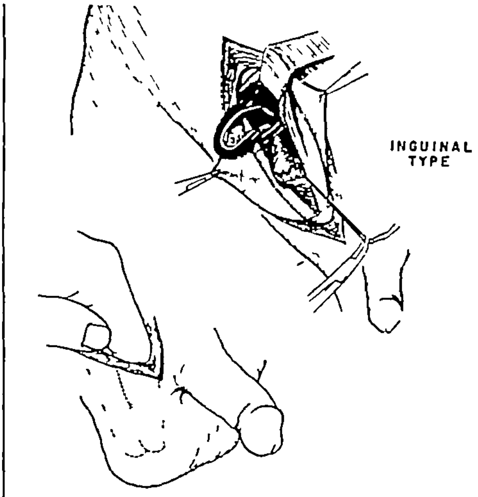


FIGURE 5



PREPARATION OF SCROTUM FOR TESTICLE

FIGURE 7

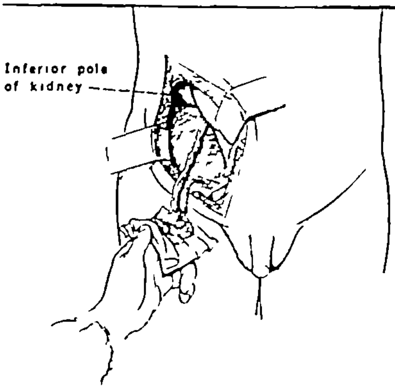


FIGURE 6

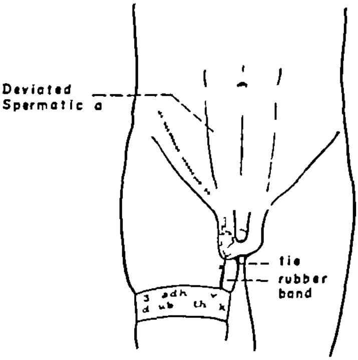


FIGURE 8

Fig 5 Spermatic surgical triangle in relation to abdominal structures
Fig 6 Abdominal exposure for high undescended testicle
Fig 7 Spermatic bundle brought down posterior to epigastric vessels without damage to vessels (inguinal or abdominal)
Fig 8 Abdominal incision closed and fixation of testicle in scrotum

The position of the testicle should be determined, if possible, before the incision is made One should be careful not to mistake a subcutaneous, undescended testis for an inguinal one A high inguinal incision is made 2 0–2 5 cm above Poupart's ligament, carried obliquely upward over the inguinal canal from the external ring to beyond the internal ring The aponeurosis of the external oblique is then incised from the external inguinal ring to above the internal, care being exercised to avoid damaging the nerves which traverse the inguinal canal The fibrous remnant of the gubernaculum, always present, is divided and mobilization of the cord proceeds Any hernial sac is recognized, freed and appropriately cared for The conjoined tendon and Poupart's ligament are cleansed and the posterior wall of the inguinal canal is thoroughly opened (fig 6)

The epigastric vessels are sufficiently mobilized to allow the testis and cord to be passed around and beneath them, to be brought out alongside the pubes at the apex of Hesselbach's triangle (fig 7) A test is made for length If additional length is needed, higher mobilization above the internal ring must be performed In this case, the light attachments to the iliac fascia which hold the spermatic vessels in their lateral position must be divided These procedures allow the medial displacement so necessary (fig 6)

For the abdominal variety of undescended testis as stated by Beltrame,[2] the incision may have to be lengthened upward and paramedially to the umbilical transverse line The peritoneum is displaced medially It is opened above the internal ring where the abdominal testis is usually found The gland is carefully dissected free from the posterior peritoneum Thus, the coalescence between the cord and the posterior peritoneal layer is interrupted, and an obstacle to the liberation of the testis is removed The vas is released medially to the seminal vesicle, and spermatic vessels released upward as far as the abdominal aorta The peritoneal opening is closed Funicolysis is considered accomplished when the inferior border of the kidney appears (fig 6)

Although the operation seems imposing and difficult, experience has proved its simplicity, safety and ultimate satisfaction The distal coverings of the cord are next removed down to the testicle No coverings should be left to form a tunic over the testicle which may later give origin to a hydrocele The greatest care, gentleness, and patience must be exercised by the operator when performing the operation

A pouch is prepared in the scrotum for reception of the testicle A nonabsorbable silk suture is securely attached to the severed gubernaculum testis or to the tunica albuginea near the lower pole of the organ (fig 7) This suture is brought out (double) through the lowest point of the scrotum and fastened to the prepared adhesive band on the thigh, with or without an interspersed rubber band, and with the desired amount of tension The testicle is thereby brought into proper position Torsion of the testicle (cord) is to be studiously avoided (fig 8)

Closure is performed as for the radical repair of direct inguinal hernia The transversalis fascia is closed The conjoined tendon and internal oblique are sutured to Poupart's (inguinal) ligament The external oblique fascia is imbricated The scrotal entrance is closed as described by Bevan, or with interrupted sutures The superficial fascia and skin are closed in the usual manner

The patient is out of bed the same evening if desired, or the following day The skin clips or sutures are removed at the usual time The tension suture and adhesive band are removed on the fifth to seventh day, later if desired The hospital discharge may be any time The testicle will remain in its new position free of tension, and *operative procedures are over for the patient*

SUMMARY

A new term has been defined and explained and a new operation for the correction of all forms of undescended testicles has been presented

The new procedure is an orcheopexy, although the new term, orchidofunicolysis, is more representative of the actual work done

Actually an evolution has taken place During a century of surgery for this condition, the best contributions of many fine surgeons, representing thousands of cases, have been retained and improved To this gradually improved technique has been added some new anatomical and mechanical, really mathematical principles

The end result is a feasible, efficient, physiological and anatomically sound procedure for surgical correction of undescended testicle, a procedure which, if more uniformly followed, would eliminate much of the dissatisfaction with present day methods

The author wishes to acknowledge grateful appreciation to Enrico Beltrame, assistant surgeon, S Martino Hospital, Genoa, R J Prentiss, R B Mullenix and J M Whisenand, San Diego, Calif for liberal use of their valuable contributions

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BILATERAL SIMULTANEOUS SEMINOMA OF THE SCROTAL TESTES

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The incidence of this specific entity is unusually rare. Except for a few remarks concerning the medical literature relating to this condition, the reader is referred to the latest (1955) review of bilateral tumors of the testicle by Abeshouse and associates.

Dodson and Hooper in 1954, in reporting 2 cases of bilateral testicular tumor (one from the literature), divided the total of 24 cases into 12 primary testicular and 12 secondary tumors. These authors further pointed out that their case of bilateral seminoma was the first and only case of bilateral seminoma, referring to the one Lewis and Priestley had previously reported in 1938 as an "adenocarcinoma" instead of seminoma. Raines and Hurdle reported a bilateral simultaneous embryonal carcinoma of the scrotal testes in 1954. Harper and associates recorded an occurrence of bilateral simultaneous seminoma in 1954. Finally, in their recent article, Abeshouse and associates referred to a total of 7 cases of bilateral simultaneous seminoma in the scrotal testes in the total series of 40 simultaneous bilateral testicular tumors (26 primary malignant, 1 primary benign, and 13 secondary malignant).

It is highly probable that other cases have not been reported, or may lie buried in the literature.

CASE REPORT

C. H. L., a 45-year-old white male store manager, was admitted to the Veterans Administration Hospital, Des Moines, Iowa, on June 27, 1955. The chief complaint was that of a swollen right testicle, of 6 months' duration. Three months prior to admission the right testicle had become painful. The patient denied having urinary symptoms, venereal disease, or any systemic disease. Mumps had occurred in 1950, with no involvement of the testes. An anal fistula had been present for 2 years. The patient was seen by a private physician 1 week prior to admission, and the patient was advised to have further investigation.

Physical examination revealed a well developed, slightly obese, plethoric white man, who was moderately apprehensive. The temperature was 98.6, pulse 100, and blood pressure 150/100. There were rough breath sounds in the left lung. The right testicle was enlarged 2 to 2½ times normal size, and felt hard and irregular. The left testicle was firm, but not enlarged. The vasa were normal. The inguinal nodes were not enlarged. A right perianal fistula was present 3 cm. directly lateral from the anal opening.

Laboratory examination revealed 5,100,000 red blood cells and a 9,900 white blood cell count, hemoglobin 15.5 gm., sedimentation rate 13, and a negative

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Read at meeting of the Iowa Urological Society on December 10, 1955 at Iowa City, Iowa.

Accepted for publication July 17, 1956.

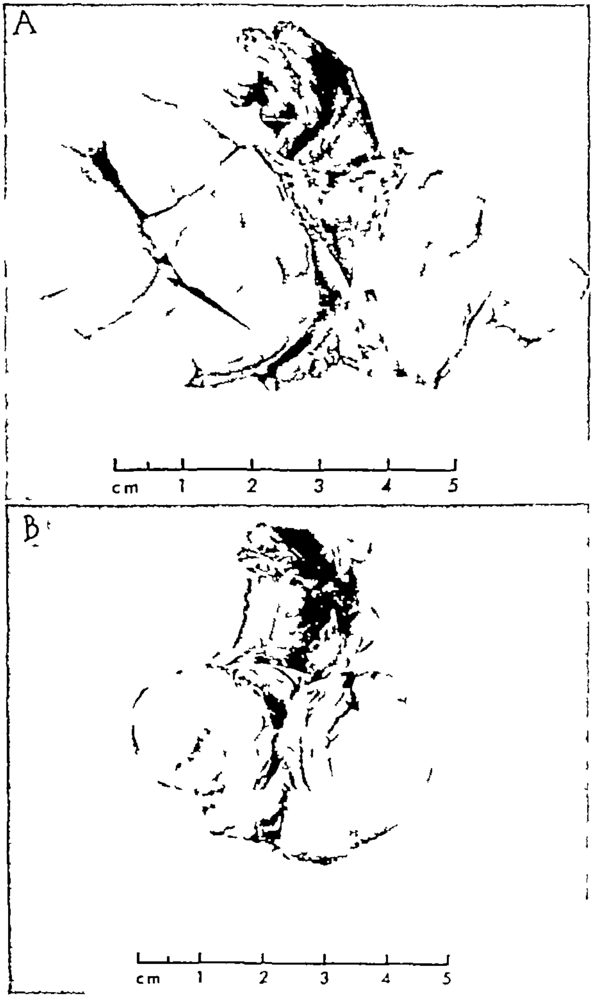

Fig 1 *A, right testicle showing replacement by seminoma B, left testicle showing replacement by seminoma*

C-reactive protein The urine was normal, serology negative, and the blood Friedman was negative The chest film and intravenous pyelogram were within normal limits without any evidence of metastasis

On June 29, 1955, a right orchiectomy and high excision of spermatic cord at the internal ring were performed The testicle was markedly enlarged and gave the appearance of malignancy Although the left testicle was suspiciously firm, it was elected to delay exploration since it was thought that inflammation might account for the induration of the scrotum and remaining contents

The left testicle did not change in character, and 15 days later, on July 14, 1955, a left orchiectomy and amputation of the spermatic cord to the internal inguinal ring were performed The testicle was not enlarged, but grossly showed complete replacement of normal tissue with seminoma Postoperatively the patient did well

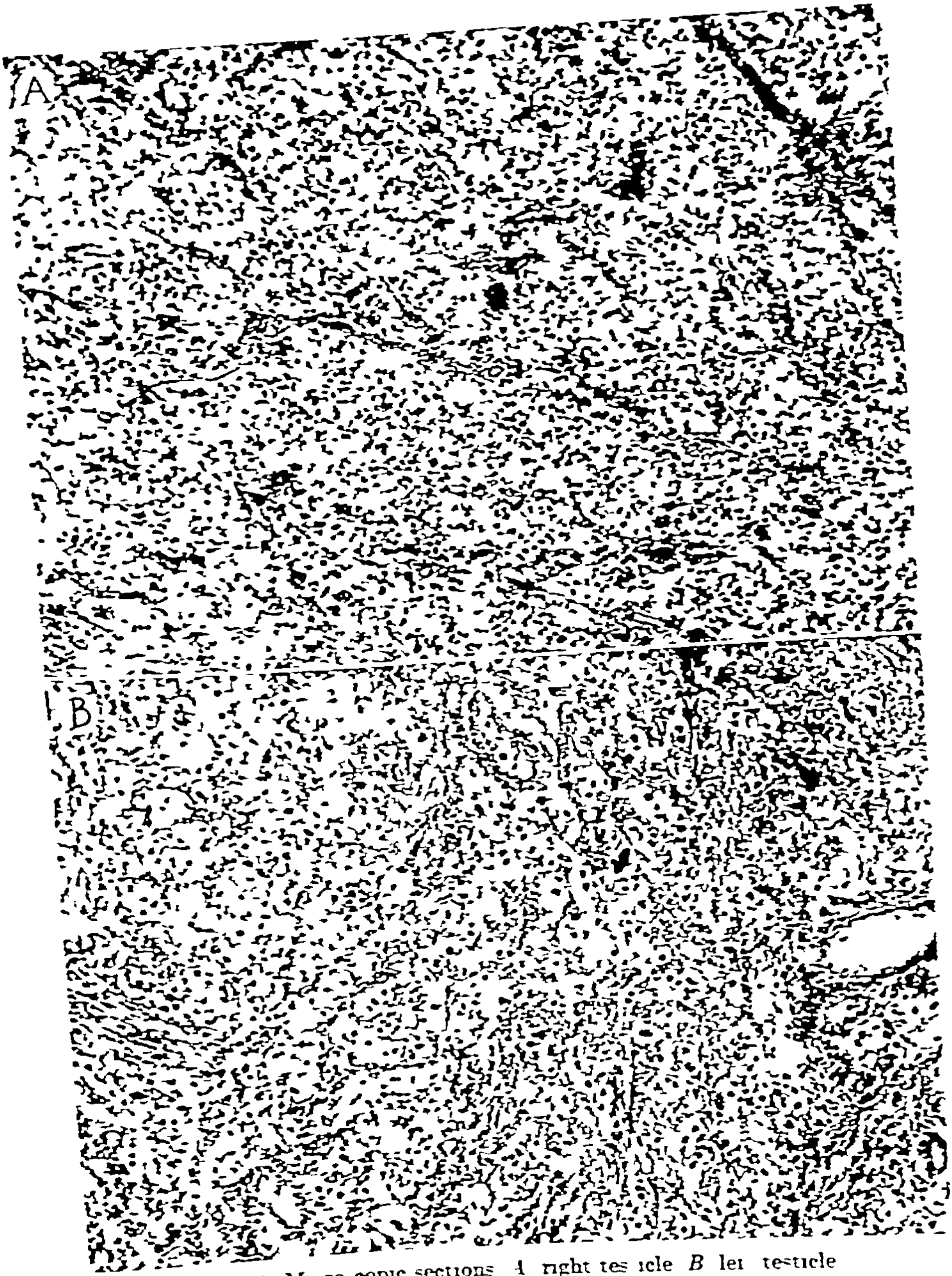

Fig 2 Microscopic sections A right testicle B left testicle

Pathology report Grossly the right testicle and spermatic cord measured 5 by 6 by 8 cm after fixation On section lobulated areas of grayish-white tissue were separated by small bands of fibrous tissue The left testicle had the same appearance on cross-section (fig 1)

The microscopic appearance of the two testicles was similar (fig 2) There was diffuse and complete replacement of seminiferous tubules and germinal epithelium by polyhedral cells with clear and large, oval hyperchromatic nuclei, having one or two nucleoli Separating the cords of epithelial cells into lobules were strands of connective tissue infiltrated by moderate numbers of lymphocytes Mitoses were relatively frequent and there were scattered areas of necrosis Diagnosis Seminoma of the testes, bilateral

Postoperatively the patient received 2,000 roentgens depth dose to both inguinal areas, opposing umbilical and lumbar areas, opposing epigastric and lower dorsal areas in 10 by 10 cm areas except the umbilical and lumbar, which was 10 by 15 cm This was administered with Friedman's technique using 200 K V, 25 milliamperes and a filtration of 0 4 mm tin, which is equivalent to 1 95 mm copper, delivered at a distance of 50 cm, in approximately six weeks

The patient was next seen on January 24, 1956, with no evidence of recurrence by chest roentgenogram or abdominal palpation He had gained 17 pounds in weight and felt fine He is to be recalled in 6 months for repeat chest roentgenogram and excretory urography

CONCLUSION

Because of the extremely low incidence of bilateral simultaneous seminoma in scrotal testes, this case is presented for addition to the literature

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TORSION OF THE APPENDIX EPIDIDYMIS AND TESTIS: REPORT OF SIX EPISODES

SAMUEL S. AMBROSE AND JOHN E. SKANDALAKIS

During the first 10 months of 1955 six episodes of torsion of the appendix testis or epididymis were observed in two hospitals in Atlanta, Georgia. Two were personal cases. Dr. Charles R. Rieser, Dr. John Akin, and Dr. J. W. Veach kindly consented to the inclusion of their cases in this report, thus bringing the total to five, of which three were accurately diagnosed preoperatively.

Ombrédanne is credited with the first report of torsion of the appendix testis. He included this case in a report on torsion of the testis in 1913.[1] Colt in 1922 was the first to accurately describe the clinical and operative findings of a case of torsion of the appendix testis.[2] Mouchet began in 1923 a series of publications which succeeded in focusing attention on this lesion.[3] Excellent summaries of the literature and case reports were published by Dix[4] in 1931, Randall[1] in 1939, and Seidel and Yeaw[5] in 1950. Although the number of reported cases is well over one hundred, our recent experience would indicate that this lesion is far more prevalent than is generally recognized. For this reason, your attention is again called to the intrascrotal congenital appendages and their propensity to undergo torsion.

ANATOMY

The appendix testis or hydatid of Morgagni,[6] which is found as a sessile but more frequently as a pedunculated structure arising from the anterior-superior surface of the testicle beneath the caput major of the epididymis, is the most common intrascrotal appendage and the most persistent müllerian vestige in the male (figs. 1 and 2). It represents a remnant of the most cephalad portion of the müllerian duct and corresponds to the fimbriated end of the fallopian tube. The size varies from 1 cm. to 1.0 cm. in diameter. Gross cystic change is rarely found, and the term, hydatid, is therefore neither descriptive nor proper in most instances. Histologic examination reveals the appendix to consist of loosely arranged connective tissue rich in blood vessels. The surface is covered with tall columnar epithelium which frequently is ciliated and quite similar to that covering the fallopian tube. Spaces within the fibrous stroma which appear to be lined with endothelium may be present. Epithelial inclusions may be present and apparently represent ducts which are lined with columnar epithelium.[6]

Read at annual meeting, Southeastern Section of American Urological Association, Hollywood Beach, Fla., March 25-29, 1956.

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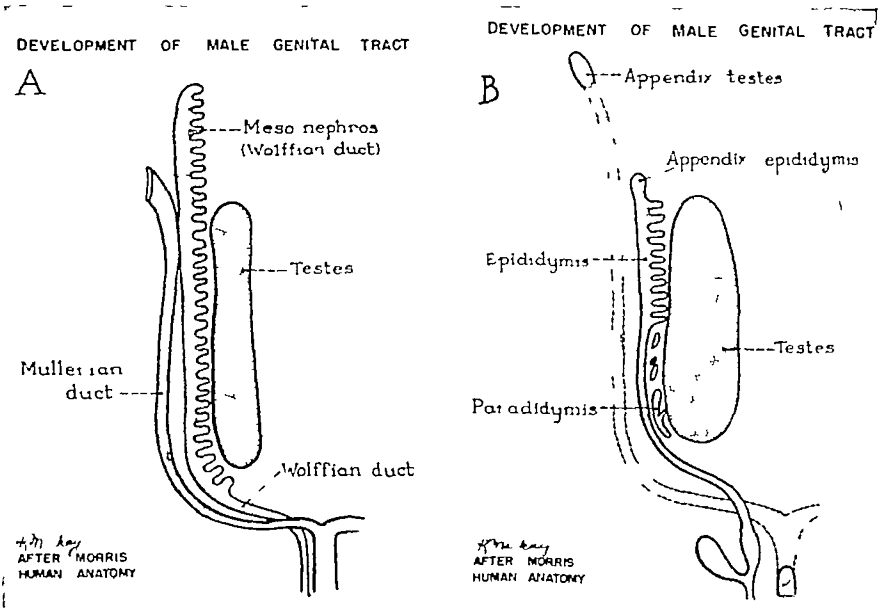

DEVELOPMENT OF MALE GENITAL TRACT
A
Meso nephros (Wolffian duct)
Testes
Mullerian duct
Wolffian duct
AFTER MORRIS HUMAN ANATOMY
DEVELOPMENT OF MALE GENITAL TRACT
B
Appendix testes
Appendix epididymis
Epididymis
Testes
Paradidymis
AFTER MORRIS HUMAN ANATOMY

FIG 1 Schematic representations A, embryonal gonad, müllerian duct, and mesonephros B, involution of the müllerian duct and mesonephros illustrating site of origin of intrascrotal gonadal appendices

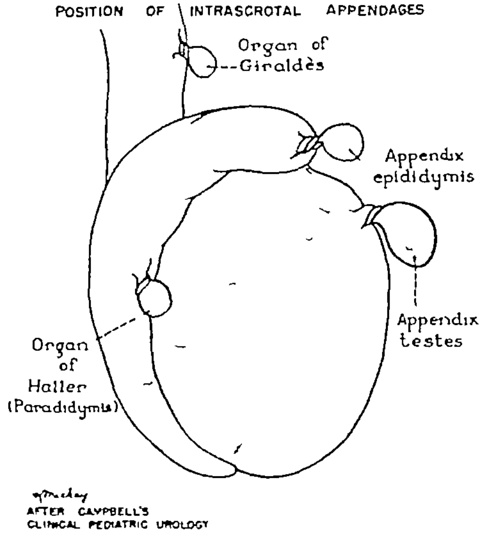

POSITION OF INTRASCROTAL APPENDAGES
Organ of Giraldès
Appendix epididymis
Appendix testes
Organ of Haller (Paradidymis)
AFTER CAMPBELL'S CLINICAL PEDIATRIC UROLOGY

FIG 2 Position of various intrascrotal gonadal appendices is demonstrated

A few leukocytes or round cells are usually found scattered throughout the stroma

The appendix epididymis is less frequently present and occurs as a pedunculated mass arising from the anterior-superior pole of the epididymis and represents a remnant of the most cephalad portion of the wolffian system or mesonephros This portion of the wolffian system is sometimes known as the epigenitalis The histologic picture is that of a fibroepithelial mass consisting of loose connective tissue which occasionally contains epithelial lined ducts The appendix is covered with a serosal membrane

The organ of Giraldes or paradidymis, which is rarely found, represents a remnant of the wolffian system and is attached by a pedicle to the first portion of the spermatic cord immediately above the caput major of the epididymis Another rare structure, the organ of Haller or paradidymis, is found attached by a pedicle to the midportion of the epididymo-testicular groove and is also a remnant of the wolffian system

The pathological change which these appendices most frequently undergo is that of torsion The exact reason why some of these structures undergo torsion while many others remain undisturbed is unknown It would appear that physical force produced by extrinsic or intrinsic factors acting upon the scrotum was necessary to cause torsion Certainly the frequent history of some trauma to the scrotum, violent exercises, or mere crossing of the legs immediately before the onset of pain cannot be ignored Spontaneous infarction could occur, but it has not been verified Torsion of these appendages most frequently occurs in the first two decades of life with the peak between 11 and 14 years of age [4]

CASE REPORTS

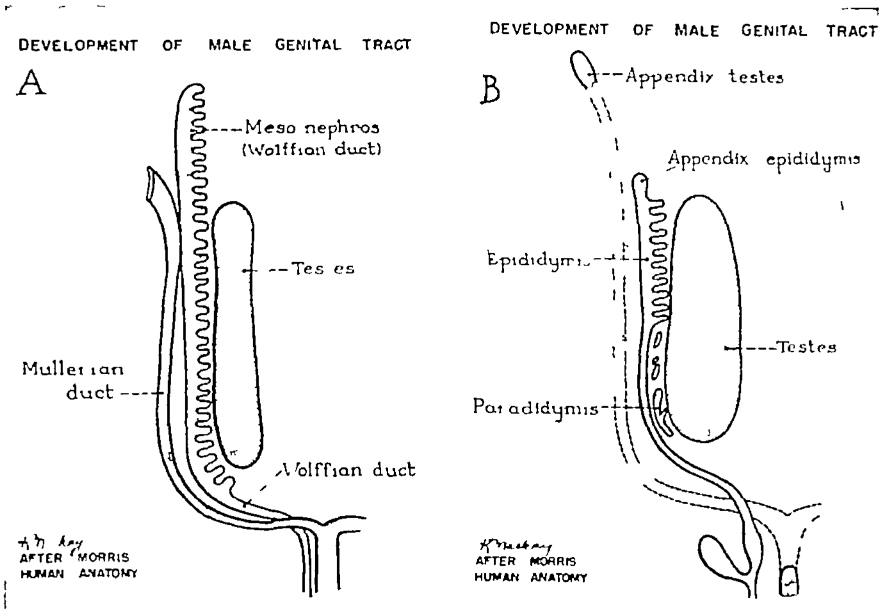
Case 1 R P, aged 13, Piedmont Hospital No 153837, was admitted January 8, 1955 Pain in the left hemiscrotum of 7 days' duration and urinary frequency without preceding injury were the presenting complaints He had received penicillin for 3 days with transient improvement Examination revealed an enlarged, red, extremely tender left hemiscrotum containing a tense, tender hydrocele Urinalysis was within normal limits The initial impression was acute epididymitis with secondary hydrocele He was treated for 3 days by terramycin with symptomatic improvement and disappearance of the hydrocele This permitted adequate palpation, and a firm, tender, 1 0 cm nodule on the anterior-superior surface of the testis, which moved in relation to the parietal tunica vaginalis but not to the testis, was noted The boy was admitted to the hospital, his temperature was 99 6F, white blood count 9,950, and urinalysis revealed no abnormalities

Preoperative impression Undetermined

On opening the tunica vaginalis, 4 to 5 cc cloudy fluid escaped A 1 0 cm blue-black necrotic mass was attached to the anterior-superior surface of the testis beneath the caput major of the epididymis The appendix was fixed to the testis by fibrinous adhesions and on elevating the appendix, a short, twisted pedicle was noted The appendix was excised and the scrotum closed with drainage Pain was relieved immediately by removal of the appendix and the patient was discharged from the hospital two days following surgery

Pathological report *This appendage is so necrotic that very little of it can be identified Around the edge there is an incomplete layer of columnar cells in a single row The central portion contains numerous leukocytes"*

Case 2 J C, aged 10 years, St Joseph Infirmary No 12740, was admitted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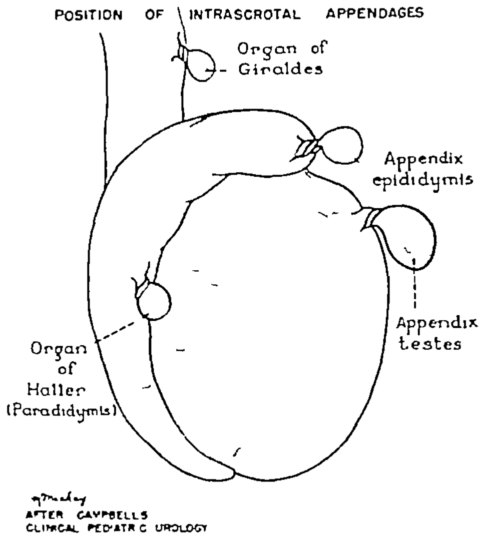
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Case 2 J C , aged 10 years, St Joseph Infirmary No 12740, was admitted

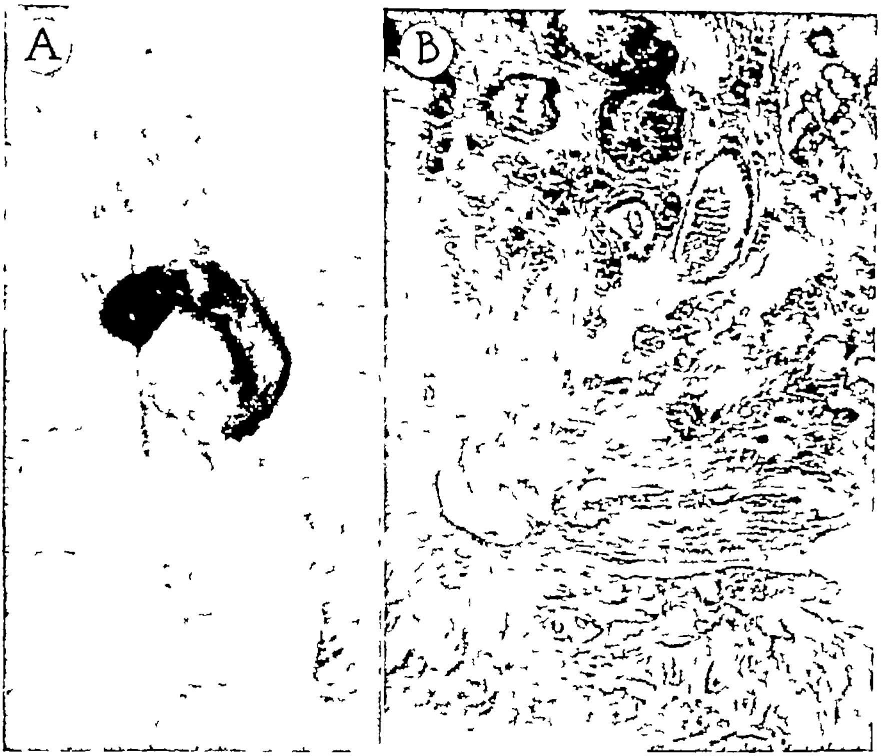

Fig 3 Case 2 *A* acute torsion of appendix epididymis *B*, calcification of epithelial, ducts of this appendix epididymis indicates chronicity

April 7, 1955 Two weeks earlier he experienced sharp, severe pain in the left hemiscrotum on crossing his legs Swelling, ecchymosis, and tenderness of the scrotum followed immediately but gradually improved during the next 2 weeks There were no other signs or symptoms Examination revealed the left testis to be slightly enlarged On the anterior-superior pole of the testis there was an 8 mm hard, tender mass which moved freely within the tunica vaginalis except for fixation to the superior pole of the testis (fig 3, *A*) On admission to the hospital, the temperature was 99 4F, hemoglobin 13 8, and white blood cells 7,800 The urinalysis was within normal limits

Preoperative impression Torsion of appendix testis or epididymis

Operative findings The tunica vaginalis contained several cubic centimeters of bloody fluid A 1 0 cm grey-black mass was attached by a short pedicle to the caput major of the epididymis which was swollen and erythematous The appendix was resected and the scrotum closed with drainage

Pathological report 'The specimen consists of a small, dark greyish tumor which has a diameter of 1 cm It appears to be pedunculated and there is evidence of a torsion of its pedicle On section it has the same greyish color, but in the center the color changes to reddish Section of epididymis shows an area of fibrosis and calcification of tubular structures (fig 3, *B*) These tubules are not definitely identified due to heavy calcium deposition This is rather an uncommon type lesion without specific designation "

The patient was discharged from the hospital free of pain 3 days following surgery

Case 3 L J aged 12 years St Joseph Infirmary No 14194, was admitted May 22 1955 (He was a patient of Dr J W Veach Jr) He gave a history of progressively more severe pain in the right testis and groin of 3 days duration beginning shortly after a fall No constitutional signs or symptoms were present The right hemiscrotum was red and swollen and within it was a tender mass larger than a normal testis but accurate palpation was impossible because of tenderness The temperature was 100F hemoglobin 15 gm and white blood cells 9 700 Urinalysis was within normal limits

Preoperative impression Torsion of testis

A small amount of bloody fluid escaped from the tunica vaginalis The testis and epididymis were edematous and inflamed The appendix testis was swollen black and attached to the testis by a twisted pedicle The appendix was excised and the scrotum closed without drainage

Pathological report This structure has a covering of epithelium which is cuboidal to columnar and in places appears to be ciliated The epithelium covers the papillomatous projections of loose connective tissue This tissue is heavily infiltrated with inflammatory cells mainly polymorphonuclear leukocytes The blood vessels in the tissue are distended and there are also areas of hemorrhage This picture is consistent with that seen in an acute torsion with beginning necrosis

The patient returned August 9 1955 (St Joseph Infirmary No 16920) Four days earlier he experienced pain in the left hemiscrotum that progressively became worse There were no other signs or symptoms The left hemiscrotum was swollen and so tender that contained structures could not be differentiated His temperature was 98 6F hemoglobin 12 5 gm and white blood cells 11 450 The urinalysis was within the limits of normal

Preoperative impression Torsion of appendix testis

The tunica vaginalis contained a small amount of turbid fluid. The appendix testis was swollen, congested and the pedicle was twisted The appendix was excised and the scrotum was closed without drainage

Pathological report Specimen is a soft deeply brown apparently encapsulated tumor mass measuring .9 by 6 by 4 cm Section shows the tissue to be covered on one surface by tall columnar epithelium Underneath this is an acute inflammatory infiltrate and hemorrhage

The patient was discharged free of pain 48 hours after surgery

Case 4 C B aged 6 years (St Joseph Infirmary No 17784) was admitted August 31 1955 (He was a patient of Dr John Akin) He gave a history of pain in the left groin and hemiscrotum of 24 hours duration associated with [illegible] of the left testis He fell from his tricycle several days prior to the onset of pain No other signs or symptoms were noted The left scrotum [illegible] and the left testis was 2–3 times normal size His temperature was 100F hemoglobin 15 8 gm and white blood cells 15 400 Urinalysis [illegible]

Preoperative impression Torsion of testis

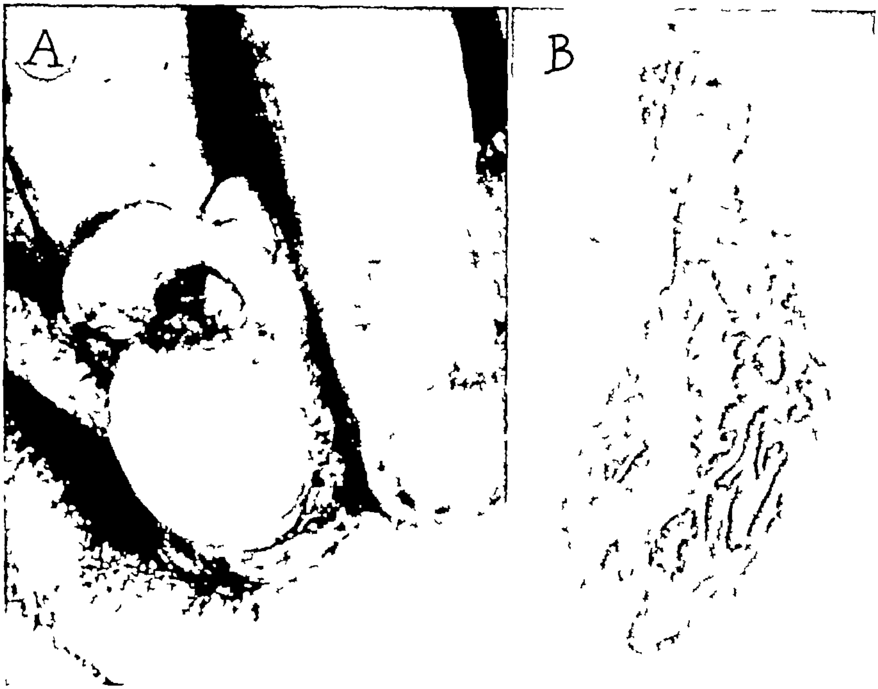

FIG 4 Case 5 *A*, torsion of appendix testis *B*, photomicrograph demonstrates inclusion of epithelial lined ducts Epithelium is similar to that of fimbriated end of fallopian tube

The appendix testis was swollen and black This was excised and the scrotum closed without drainage

Pathological report "This specimen consists of an oval, greyish-brown piece of tissue which measures 8 by 4 cm Sections show a tissue which is covered by columnar type epithelium The tissue underlying this is composed of markedly dilated vessels and acute inflammatory cells "

The patient was discharged free of pain 36 hours after operation

Case 5 W W, aged 12 years (St Joseph Infirmary No 19326), was seen October 14, 1955 (He was a patient of Dr Charles R Rieser) He gave a history of pain in the right groin of 3 days' duration followed by swelling of the right hemiscrotum The pain was mild and there were no constitutional symptoms The scrotum was red and edematous over the right side The testis was slightly indurated and tender The temperature was 97F, hemoglobin 14 4 gm , and white blood cells 12,000 Urinalysis was within normal limits

Preoperative impression Torsion of appendix testis

The scrotal tunics were acutely inflamed The appendix testis was blue-black in color, and the superior pole of the epididymis was slightly enlarged and erythematous (fig 4, 4) The testis was normal The appendix was excised and the scrotum closed with drainage

Pathological report "This specimen consists of a soft, deep reddish-tan, irregular portion of tissue which measures 1 by 6 by 4 cm Section shows the tissue to be composed largely of an acute inflammatory infiltration and interstitial hemorrhage limited by a benign columnar type epithelium" (fig 4, *B*)

The patient was discharged free of pain 3 days following surgery

DISCUSSION

The clinical picture is one primarily of pain either beginning in the affected hemiscrotum or groin shortly after vigorous exercise, trauma, or crossing the legs On occasion this pain has apparently begun spontaneously without any known predisposing manipulation of the scrotum The pain is usually rather mild initially and in most instances is much less severe than with torsion of the testis Constitutional symptoms such as fever, malaise, nausea, vomiting, or prostration are rarely noted, and associated urinary tract symptoms are unusual Shortly after the onset of local pain, swelling and erythema of the overlying tunics of the scrotum appear If untreated the pain has been known to exist as long as three weeks, but the entire duration of pain is not known because a diagnosis has not been established in unexplored cases

Physical examination usually reveals swelling of the hemiscrotum with exquisite local tenderness The overlying scrotal skin may be red and shiny from edema and inflammatory reaction A hydrocele quickly accumulates in most instances and obscures the landmarks which make the diagnosis obvious on palpation If the patient is seen before a hydrocele develops or if the fluid has been aspirated, the affected appendage can be palpated as a small, firm mass attached to the anterior-superior pole of the testis or epididymis The lesion moves freely within the tunica vaginalis except for its attachment to the testis or epididymis by its pedicle After several days, it may become adherent to the surface of the testis or epididymis by fibrinous exudate and simulate a mass arising directly from these structures Transillumination of the hydrocele may show a dense mass lying on the surface of the testis or epididymis Studies of the peripheral blood and urinalysis rarely reveal any abnormalities

At operation, serous or serosanguinous fluid may be present in the tunica vaginalis The affected appendix presents itself as a dark grey to blue-black, firm mass attached to the testis or epididymis by a short, twisted pedicle The serosa immediately surrounding the pedicle and the caput major of the epididymis may be inflamed and edematous If the lesion is old, there may be fibrinous or fibrous adhesions between the necrotic mass and the surface of the testis or epididymis

The histopathological findings are those of acute inflammation and varying degrees of infarction As one would expect this is usually a red infarct On rare occasions calcification may appear within the substance of the appendage indicating prolonged inflammation and possible recurrent, incomplete torsion[7]

The prolonged incapacity caused by the persistent pain associated with torsion of these appendices is alone adequate indication for surgical excision The immediate relief of pain and prompt return of the patient to full activity is convincing evidence that excision is justified It has been suggested that the appendices of the opposite testis be removed when the affected appendix is excised The case presented here of bilateral torsion occurring at an interval of several months would support this suggestion

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[7] Rolnick, H C Torsion of the hydatid of Morgagni J Urol, 42 458–462, 1939

The diagnostic difficulty encountered is usually that of failure to consider torsion of the intrascrotal appendices Acute epididymitis, torsion of the testis, orchitis, acute hydrocele, and strangulated hernia are those conditions most frequently considered in the differential diagnosis The absence of fever, evidence of infection of the lower urinary tract, or an acute infection elsewhere in the body would make the diagnosis of acute epididymitis unlikely Orchitis in the absence of mumps or other viral disease would be extremely unusual Torsion of the testis is associated with extreme local pain, and systemic reaction such as prostration is more evident than in cases of torsion of the appendix testis or epididymis Absence of signs and symptoms suggesting intestinal obstruction would suggest a lesion other than an incarcerated hernia

SUMMARY

Six episodes in five individuals of torsion of the appendix epididymis or testis are presented and the clinical entity discussed

Our experience would indicate that torsion of the intrascrotal appendices is a frequently overlooked, misdiagnosed, not uncommon lesion which is not getting its due attention from our profession

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TUMOR OF THE TUNICA VAGINALIS TESTIS: CASE REPORT OF NEURILEMMOMA

ROBERT COWEN

Florence Crittenton Hospital, No. 70689-C. A 67-year-old white man, G. B., was admitted November 10, 1955 for cardiac failure. A previous admission on November 19, 1953 had shown bilateral nephrolithiasis, duodenal ulcer, arteriosclerotic heart disease and a hard, not tender scrotal mass approximately 5 by 5 cm. The present status was the same except for pleuritic effusion and cardiac decompensation and a somewhat larger scrotal tumor. The nonprotein nitrogen determination was 63, hemoglobin 98 per cent, blood phosphorus 5.2, albumin 2 plus, anterior pituitary-like excretion negative, and ketosteroids within normal limits.

After the acute symptoms subsided and because the patient insisted that the tumor be removed, operation was performed.

Under local anesthesia, the neoplasm which was discrete from the right testicle and epididymis and lined with heavy intact coverings of tunica, with a moderate amount of hydrocele, was excised with the entire tunica, leaving a normal appearing testis and epididymis. The size of a clenched fist, the nodules showed a consistency of cartilage. The preoperative impression was teratoma of the tunica vaginalis, the postoperative diagnosis was adenomatoid tumor (teratoma).

Pathology report. The gross specimen was an ovoid mass 7.5 by 5 by 5 cm. The capsule was shaggy and a portion of skin was attached. On section there was within the capsule a myxomatous stroma with irregular ovoid nodules. These well circumscribed nodules were gray and yellow.

Microscopic study. Sections of the tumor showed nodules imbedded in loose connective tissue stroma. The nodules were well circumscribed and had a varied appearance, for the most part composed of interlacing bundles of elongated cells resembling fibroblasts and fibrocytes with palisading of the nuclei. Areas with suggestion of Verocay bodies were noted. The larger nodules showed myxomatous tissue replacement. Special stains showed the neurogenic origin of the tumor. Van Giesen stain showed yellowish filter staining, Maison trichrome stain showed reddish stain. The cells of these tumor nodules exhibited considerable variation, particularly of the nuclei which showed a marked variation in size, shape, and staining quality. Diagnosis: Neurilemmoma of tunica vaginalis testis (schwannoma) (fig. 1). E. S. Zawadski, pathologist.

DISCUSSION

Neurilemmoma, or neurinoma, or perineural fibroblastoma, arises from the sheath of Schwann, most often from a peripheral nerve. The first cases of retroperitoneal neurilemmoma adjacent to the kidney, one being benign and the other malignant, have been reported.[1]

Accepted for publication July 19, 1956.

[1] Deming, C. L. and Newman, H. R.: J. Urol., 72: 316, 1954.

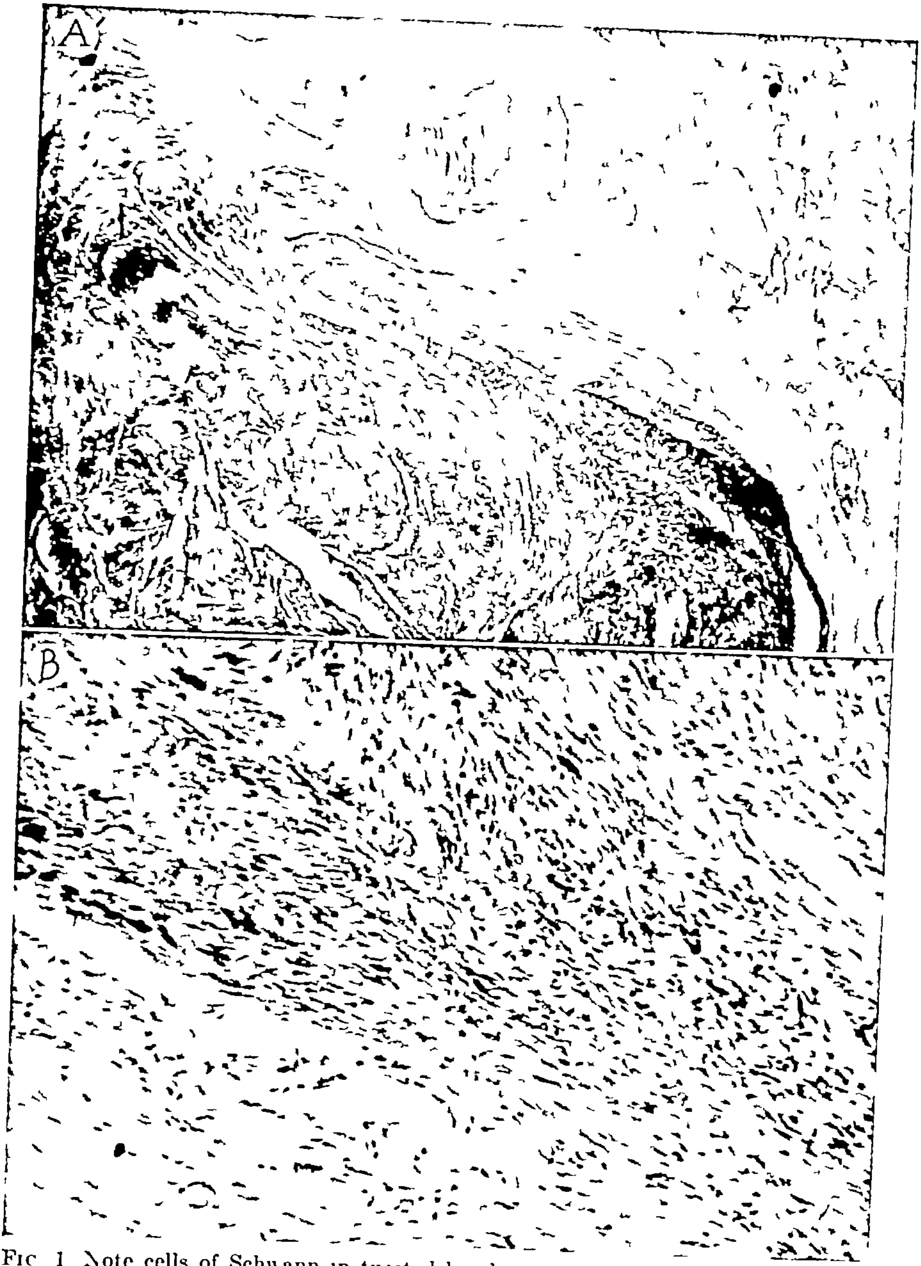

FIG 1 Note cells of Schwann in twisted bands or cords accompanied by connective tissue fibers, long narrow, elongated nuclei, interweaving and palisading in a whorl like arrangement, Verocay bodies in arrangement of tactile corpuscles

If this type of tumor arises from mesodermal connective tissue it is called fibrosarcoma Fascicular and reticular types may be found together The fascicular type has parallel intercellular fibers and the reticular has a disorderly arrangement of a loose meshwork of cells of variable shape and intercellular networks containing mucinous fluid staining blue Pigmented fibers and collagen are scanty in the fascicular group

Retroperitoneal neuroblastoma invading the ureter has been reported in a child,[2] neurilemmoma in the renal hilus[3] Neurofibromatosis of the bladder has been reported in 14 cases, nine of which were associated with Von Recklinghausen's disease[4] The slides all showed the palisading characteristics of the growth and conclusions are that neurofibromatosis of the bladder must be considered in all cases of Von Recklinghausen's disease

In a report of an intrascrotal adenomatoid tumor[5] with lymphoid or epithelial elements in dispute, it was considered to be of mesonephric remnants Wessel,[6] in a review of 251 tumors of the spermatic cord going back to Cloquet in 1819, reported that 81 were malignant, and the total was brought to 288 No epithelial cells were recorded and the mesoblastic cells were lipoma, fibroma, myxoma, vascular lymphangioma, and heterogeneous or dermoid cyst, the malignant were epthelial, none, mesoblastic sarcomyxoma, chondro, fibro-, and spindle cell Heterogeneous teratoma included seminoma of Chevassu

A huge benign fibroma of the tunica vaginalis was reported in 1949[7] and a casual review of the most exhaustive study of benign tumors of the small intestines showed that in 1399 cases, the tumors were neurogenic in 90 instances[8]

SUMMARY

A case of neoplasm of the tunica vaginalis testis, grossly typical of cartilagenous teratoma is presented, which pathologically is classical of neurilemmoma or schwannoma

Review of the recent literature shows renal and retroperitoneal, but no intrascrotal tumor, derived from adventitia of the peritoneum or retroperitoneal area

Neurogenic tumors of the intestine being relatively frequent it is remarkable that schwannoma of the tunica vaginalis has not been previously found

28 W Adams St, Detroit 26, Mich

[2] Beneventi, F A and Twinem, F P J Urol, 60 235, 1948
[3] Phillips, C A S and Baumrucker, George J Urol, 73 671, 1955
[4] DeKlerk, Johan and Campbell, W A J Urol, 72 1167, 1954
[5] Curtiss, Charlotte and Hock, Ernest J Urol, 76 292, 1956
[6] Wessel, H N J Urol, 69 823, 1953
[7] Kawachi, George J Urol, 62 61, 1949
[8] River, Louis Surg, Gynec & Obst, 102 1-38 (Internat Abstr Surg) 1956

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A STUDY OF 229 CONSECUTIVE CASES OF TOTAL PERINEAL PROSTATECTOMY FOR CANCER OF THE PROSTATE

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This paper presents 274 consecutive total perineal prostatectomies for suspected malignancy of the prostate gland The surgery was performed between January 1, 1930 and December 31, 1955 for the most part by the senior author The data were analyzed with the help of I B M punch cards, sorters and tabulators for comparative study Of these 274 cases, 39 were rejected as the microscopic sections failed to disclose malignancy and 4 were rejected because the pathologic reports were missing One primary carcinoma of the seminal vesicle was rejected and one primary bladder tumor invading the prostate was rejected The two hundred and twenty-nine remaining cases will be presented here for analysis

Jewett's careful and critical evaluation of the results of radical perineal prostatectomy for cancer of the prostate[1] [2] has firmly established the soundness and value of this operation as first conceived and executed by Hugh Young[3] [4]

The modified technique employed in the 229 cases analyzed here is described by Belt[5] and differs from Young's original concept of the operation in several ways

1) The approach through the perineum is between the rectum and the anal sphincters[6]

2) No bladder cuff is routinely removed unless there is invasion into the bladder neck In three cases the extension involved the ureteral orifices necessitating excision of the trigone and reimplantation of the ureters The ureters were splinted for 1 week by ureteral catheters which lay in the urethra within the indwelling Foley catheter

3) Prior to 1946 a small portion of the apex (less than 1 cm) of the prostate, as originally described[5] was left in, in an effort to avoid injury to the external sphincter and prevent incontinence Since 1946 the entire prostate, seminal vesicles, ampullae and several centimeters of the vas deferens have been removed If Denonvilliers' fascia, over the seminal vesicles, strips off easily it is removed with the gland

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Read at annual meeting, American Urological Association, Boston, Mass , May 31, 1956

[1] Jewett, H J Radical perineal prostatectomy for cancer of the prostate An analysis of 190 cases J Urol , 61 277–280, 1949

[2] Jewett, H J Radical perineal prostatectomy for carcinoma, an analysis of cases at Johns Hopkins Hospital, 1904–1954 J.A.M A , 156 1039–1041, 1954

[3] Young, H H The early diagnosis and radical cure of carcinoma of the prostate Being a study of 40 cases and presentation of a radical operation which was carried out in 4 cases Johns Hopkins Hosp Bull , 16 315–321, 1905

[4] Young, H H The cure of cancer of the prostate by radical perineal prostatectomy (prostato seminal vesiculectomy) History, literature and statistics of Young's operation J Urol , 53 188–253, 1945

[5] Belt, E Radical perineal prostatectomy in early carcinoma of the prostate J Urol , 48 287–297 1942

[6] Belt, E , Ebert, C E and Surber, A C A new anatomic approach in perineal prostatectomy J Urol , 41 482–497, 1939

4) The bladder neck is anastomosed directly to the urethra around a Foley catheter by four quadrant sutures [6]

These differences have been criticized by Young[4] and others as making the procedure less radical.

PREOPERATIVE MANAGEMENT AND PREOPERATIVE ORDERS FOR PERINEAL PROSTATECTOMY

In the routine workup of a patient before prostatectomy the following procedures are included serum acid phosphatase (total and prostatic fractions), serum alkaline phosphatase, an anteroposterior flat x-ray film of the abdomen, nonprotein nitrogen, urea nitrogen, excretory urography, routine urinalysis, Gram stain of urine, phenolsulfonphthalein, biopsy when indicated and cystoscopy are all carried out ahead of the immediate preoperative orders A marked effort is made to hydrate the patient orally during the days leading to surgery

Immediate preoperative orders

1) Routine urinalysis and Gram stain

2) A cleansing enema is given the night before and the morning of the operation

3) A surgical preparation of the scrotum, genitalia and perineum is done the night before

4) A light diet the evening before surgery Breakfast is omitted the day of the prostatectomy

5) Complete blood count, routine urinalysis, bleeding time and coagulation time are done

6) The patient is typed and cross matched to have one unit of blood available in the surgery

7) If there is no sensitivity the patient is given 1 gm streptomycin and 400,000 units of penicillin intramuscularly the evening before the operation

POSTOPERATIVE MANAGEMENT

1) The patient is ambulated within 24 hours

2) The Penrose drain is removed in 24 hours At this time all perineal dressings are also removed

3) The catheter is removed in 8 days, provided the bowels have moved, the wound has healed, there is no perineal drainage and there is no hematuria following the first bowel movement

4) Dry heat (infra red) is applied routinely for 20 minutes, 3 times a day to the perineum after the dressings and drain have been removed

5) Hot moist dressings are applied 3 times daily if the wound edges show evidence of inflammation

6) If there is perineal drainage, hot sitz baths b.i d are instituted

7) Low residue diet and a constipating regimen for 8 days are used On the eighth day the bowels are moved with 1 ounce of milk of magnesia and 2 drachms of cascara and two to three ounces of warm mineral oil instilled into the rectum

8) If there is no sensitivity the patient is routinely placed on 1 gm streptomycin and 400,000 units of penicillin daily for 5 days Following this the patient

is placed on a sulfonomide therapy of choice q i d , until the urine is free of pus and bacteria

9) A closed system for irrigation with saline is made available but is used as little as possible and only to test for and insure drainage

METHOD OF FOLLOWUP

The patients who have a diagnosis of malignancy of the prostate gland are followed very carefully A form sheet is used in our office charts with these patients in an effort to avoid omissions in observation

ELMER BELT UROLOGIC GROUP
1893 Wilshire Boulevard, Los Angeles 57, Calif
Routine Postoperative Prostatectomy Check Up

General appearance
State of patient since last visit

Present weight
Weight loss? Back pain?
Is patient taking estrogenic hormone? Type of hormone and dosage
If not, reason and date stopped
Urination D__________ Stream__________ Hematuria__________
N
Residual urine__________ Dysuria__________ Control__________
Blood pressure
Total serum acid phosphatase
Total serum alkaline phosphatase
Prostatic fraction acid phosphatase
pH______ Alb______ Sug______ Sp gr ______ ______RBC ______Hgb
WBC______ RBC______ Orgs ______ Epith______ ______WBC ______C I

Findings upon rectal palpation

Flat anterior-posterior x-ray study of the abdomen

This is so important that we prefer to follow each patient ourselves in our own office This permits an accurate early assessment of evidence of recurrence If the patient returns to his local doctor or family physician for followup care, these forms are mailed to his doctor with a request that they be returned to us for an analysis of the doctor's observations

RESULTS IN 229 CASES

A) Five-year survival in 131 cases (all stages of carcinoma and extent, table 1) One hundred and thirty-one patients, operated on prior to December 31, 1950, have been followed 5 years or more An additional 98 patients were operated on between December 1950 and December 31, 1955 Fifty-six (43 per cent) of the 131 patients followed 5 years or more, lived or are living without evidence of recurrence or metastases Thirty-two of these patients had postoperative estrogen therapy

B) Ten-year survival in 68 cases (all stages of carcinoma and extent, table 2) Fourteen (21 per cent) patients, of 68 operated on prior to December 31, 1945,

TABLE 1

FIVE YEAR SURVIVAL 1930 – 1950
(131 CASES FOLLOWED 5 YRS OR MORE)

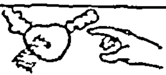
	NUMBER FOLLOWED	NUMBER SURVIVED 5 YRS WITHOUT CA	%
ALL STAGES RECTAL →	131	56	43
RECTAL CONFINED	62	39	63
MICROSCOPIC CONFINED	42	32	76
MICROSCOPIC BEYOND	34	15 *	44
SIMPLE PERINEAL[8] 81 PATIENTS HAD CA IN 1694 SIMPLE PERINEAL PROSTATECTOMIES	75 **	32	42 7 %

* TWELVE IN CAPSULE BUT NOT BEYOND EIGHT HAD LOCAL RECURRENCE OR METASTASES

** IN FOUR CARCINOMA WAS TOO EXTENSIVE, FIXED FOR TOTAL

TABLE 2

TEN YEAR SURVIVAL 1930 – 1945
(68 CASES FOLLOWED 10 YRS OR MORE)

	NUMBER FOLLOWED	NUMBER SURVIVED 10 YRS WITHOUT CA	%
ALL STAGES RECTAL →	68	14	21
RECTAL CONFINED	35	12	34
RECTAL BEYOND 	24	6	25
SIMPLE PERINEAL[8] 81 PATIENTS HAD CA IN 1694 SIMPLE PERINEAL PROSTATECTOMIES	36	6	17 7

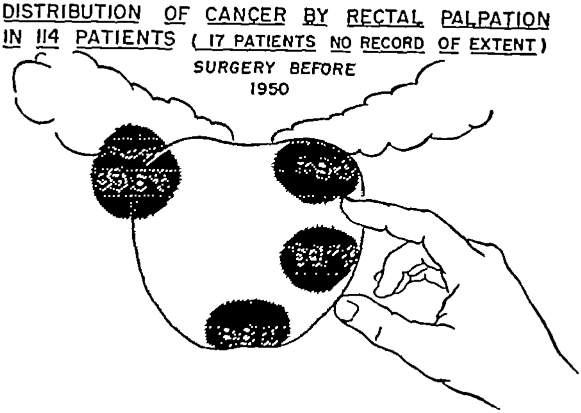

DISTRIBUTION OF CANCER BY RECTAL PALPATION
IN 114 PATIENTS (17 PATIENTS NO RECORD OF EXTENT)
SURGERY BEFORE
1950

FIG 1

lived or are living 10 years or longer, without evidence of recurrence or metastases These figures compare favorably with those in a previous report by the senior author[6] and those reported by Jewett,[1] [2] Barnes,[7] Hinman,[8] Colby[9] (see table 15)

OVERALL DISTRIBUTION OF MALIGNANCY IN PROSTATE BY RECTAL EXAMINATION IN 114 CASES

In 17 cases no record of extent is available (fig 1) The following figures represent 5-year followups or longer

	per cent
Malignancy in apex	8 8
Malignancy in base	7 9
Malignancy in lateral lobe	50 7
Malignancy involving capsule and thought to be beyond	33 6

MICROSCOPIC PATHOLOGICAL FINDINGS

A fairly close correlation between the microscopic grading on biopsy and final paraffin section was found Compare table 3 with table 6 There was a tendency on biopsy to underestimate the degree of malignancy in the rapid frozen section

HOSPITAL MORTALITY IN 229 CASES

The overall 25-year hospital mortality rate (9 deaths, 3 9 per cent) showed that eight deaths were based on a nonurological etiology (table 4) Four deaths occurred in the period 1930–1939, between 1946 and 1955, 3 deaths occurred in a total of 161 cases (1 86 per cent)

PREOPERATIVE ESTIMATED RECTAL SIZE IN 229 CASES

These figures are available in table 5

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[7] Barnes, R W Results of palliative treatment of early carcinoma of the prostate J Urol, 70 489–490, 1953

[8] Hinman, F, Jr The early diagnosis and radical treatment of prostatic carcinoma Calif Med, 68 338, 1948

[9] Colby, F Carcinoma of the prostate Total perineal prostatecomy Surg Clin of N Amer, 27 1307–1311, 1947

TABLE 3 *Microscopic surgical pathology (graded)*
(152 graded, 77 carcinoma ungraded)*

Adenocarcinoma, grade 1	11 2%
Adenocarcinoma, grade 2	49 4%
Adenocarcinoma, grade 3	25 1%
Adenocarcinoma, grade 4	1 9%
Squamous metaplasia†	12 4%

* 2 cases of sarcoma were placed in the ungraded carcinoma group

† All cases reported as squamous metaplasia in the final pathological specimen had had estrogen therapy prior to surgery Preoperative estrogen therapy is given in selected cases as an adjunct for diagnostic purposes, or for reducing the size of the neoplasm before surgery, or when malignancy had been diagnosed on previous biopsy and estrogen therapy started elsewhere

TABLE 4 *Hospital mortality (229 cases)*
Nine died in the hospital which is a mortality of 3 9% No patients died on the operating table

Certificate Causes of Death	
Shock	1
Pulmonary emboli	2
Cerebral embolus	1
Cardiovascular	3
Ruptured aneurysm	1
Pneumonia	1

TABLE 5 *Size*

Rectal	Group 1 (10 to 25 gm.)	19%
	Group 2 (26 to 50 gm)	43%
	Group 3 (51 to 100 gm.)	30%
	Group 4 (more than 100 gm)	8%

77 PREOPERATIVE BIOPSY REPORTS IN 229 CASES

In these 77 cases a previous transurethral resection or open perineal biopsy had been accomplished (table 6)

One transurethral resection biopsy was reported as benign prostatic hyperplasia microscopically but the clinical impression of malignancy was substantiated by total perineal prostatectomy Two open perineal biopsies by rapid frozen section were reported benign, but clinical and surgical judgement led to total perineal prostatectomy Malignancy was found microscopically in each case

POSTOPERATIVE DEVELOPMENT OF METASTASES IN 229 PATIENTS

Thirty-nine (17 per cent) patients had known metastases (demonstrable by x-ray) or recurrence (table 7) Twenty-three of these had metastases and 22 developed local recurrence Eight cases had both metastases and local recurrence Six patients required transurethral resection for recurring obstructive malignancy In one patient in whom recurrent malignancy was suspected, the trans-

TABLE 6 *Biopsy pathology*

Pathology Report	Grade	Cases	Per Cent
Adenocarcinoma	1	9	32 2%
Adenocarcinoma	2	13	46 4%
Adenocarcinoma	3	5	17 8%
Adenocarcinoma	4	1	3 6%
Carcinoma ungraded		46	
Benign prostatic hypertrophy		3 (before total perineal prostatectomy)	

TABLE 7 *Postoperative development of metastases in 229 patients*

Thirty nine Patients with Metastases 17%	Number of Cases	Lived 5 Years or More
Estrogen therapy	21	11
Neither estrogen nor orchiectomy	18	6
Orchiectomy & estrogens	7	3

TABLE 8 *Squamous metaplasia*

Survival	Year of Surgery	Number of Patients	Age at time of Surgery
6–7 years	1949, 48	2	57, 64
5	1950	3	64, 66, 63
4	1951	2	60, 51[b]
3	1952	3	36, 78[a], 67
2	1953	4	64, 63, 68, 47[a]
1	1954	3	81, 74, 63
Less than 1	1955	1	59

urethral resection specimen revealed fibrous tissue In six of the 8 patients who had both metastases and local recurrence, the original microscopic report showed capsular or extracapsular invasion

PREOPERATIVE ESTROGEN THERAPY IN 18 CASES WITH POSTOPERATIVE MICROSCOPIC REPORT OF SQUAMOUS METAPLASIA

This analysis includes the 229 cases to December 31, 1955 All of the 18 patients who had a final microscopic diagnosis of squamous metaplasia had estrogen therapy preoperatively (table 8) Four also had estrogen therapy postoperatively two[a] (table 8) had no recurrence, and one[b] had local recurrence The one with both local recurrence and metastases died in less than 5 years Pathological reports with a diagnosis of squamous metaplasia did not occur in any cases of this study until 1949, after estrogens had been in clinical use

OPERATIVE AGE OF PATIENTS IN WHOM METASTASES OR RECURRENCE DEVELOPED, 229 CASES

These data are included in table 9

PROSTATECTOMY

The principal problems in prostatic surgery arise as a consequence of the type of operation and the advanced age of the patients The relief of pain is complicated because adequate analgesic doses of opiate derivatives and synthetics often produce an undesirable narcosis for as long as 24 to 48 hours As a result, the elderly patient is virtually immobilized during this period, and as has been so frequently demonstrated, such immobilization increases the danger of serious vascular accident and pneumonia Other undesirable effects of opiates include nausea, vomiting, abdominal distention, constipation and, occasionally in narcotic-sensitive individuals, actual excitation

The second problem that is of considerable importance in the postoperative period is that of hemorrhage Considerable bleeding occurs in all cases of prostatectomy regardless of the local hemostatic measures employed and dangerous bleeding with shock are not uncommon In the aged and chronically ill, the danger of such bleeding cannot be underestimated The type of operation, the extreme vascularity of the prostatic bed and the poor condition of the vascular walls are unavoidable hazards in prostatectomy

Another postoperative problem is delayed healing with persistent infection of the raw prostatic bed, causing morbidity for prolonged periods

Pain Eighty-six consecutive cases having a 1-stage suprapubic prostatectomy were included in this study Fifty of these comprised a control group receiving the usual pre- and postoperative morphine, scopolamine and barbiturates, while a second group of 36 cases received n-butanol instead The observations upon postoperative pain during the first 4 days are shown in figure 2, *A*

In the operative technique employed, a Ravich hemostatic bag was kept under tension for 3 to 4 hours postoperatively During this period, the pain was often not adequately controlled by any method However, it will be noted that 36 per cent of the control group as compared with 8 per cent of the n-butanol treated group had severe pain during the day of operation On the first postoperative day, 4 per cent of the control group still had severe pain and 68 per cent had moderate pain, whereas only 17 per cent of the n-butanol group had moderate pain and none had severe pain The improved control of pain is seen to continue through the remainder of the period of observation

In this study, pain was adequately controlled by n-butanol in a higher percentage of cases than by the usual opiates employed This is of extreme interest since n-butanol does not apparently control pain through its effect on the central nervous system It has been found that in the presence of an acid pain, n-butanol may increase the pain

Experience in other clinical studies clearly indicate that the relief of pain is not psychogenic These observations suggest that the relief of pain was the result of a local effect of n-butanol upon the painful post-traumatic inflammatory process in the region of the prostatic bed

The fact that n-butanol relieves pain sufficiently has several important clinical advantages The patients come to the operating room in an alert state, but accept spinal anesthesia very well Instead of the deeply narcotized, almost semiomatose condition in which these aged men are often brought into the operating oom, they are alert throughout, and after operation, and are able and willing be ambulated on the first postoperative day without exception The annoying roblems of nausea, vomiting, abdominal distention and constipation are considerably reduced The fact that they are not entirely eliminated indicates that

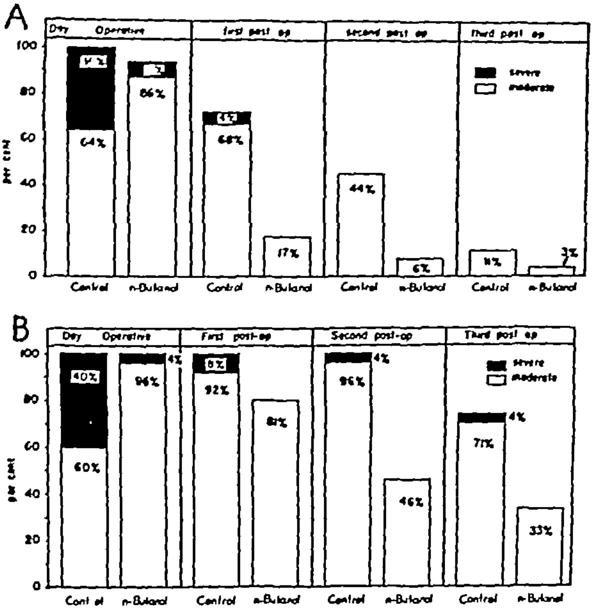


Fig 2 *A*, postoperative pain *B*, postoperative bleeding

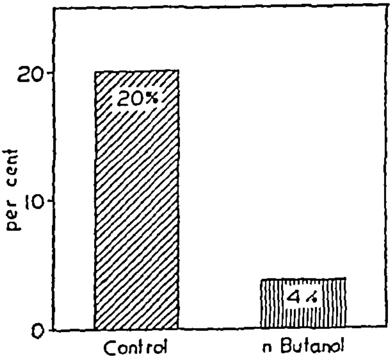


Fig 3 Transfusion

opiates increase the incidence, but are not solely responsible for these disturbances

Bleeding Two series of cases were compared from the standpoint of the severity of postoperative bleeding Twenty-five cases are included in the control group and 24 cases in the group treated with n-butanol The other 37 cases are not included because the oxidized gauze (Johnson and Johnson) employed for local hemostasis did not alter the results The degree of bleeding was judged by the color and amount of blood observed in the drainage through the suprapubic wound and urethral catheter (fig 2 *B*), as well as by the number of cases requiring one or more transfusions for actual or impending shock, at some time during the postoperative period (fig 3)

It can be seen from figure 2, *B* that severe bleeding was definitely minimized in the n-butanol treated group Only 1 case (4 per cent) had bleeding of any severity and it was this patient who required the only transfusion in this group of cases Forty per cent of the control cases had severe bleeding on the day of operation and in 20 per cent, bleeding was so severe as to require one or more transfusions during the postoperative period While a moderate degree of bleeding persisted in the majority of cases through the first postoperative day, differences in the degree of bleeding became increasingly evident by the second postoperative day By this time, less than one half of the n-butanol treated patients had a significant amount of bleeding All of the control series still had moderate to severe bleeding

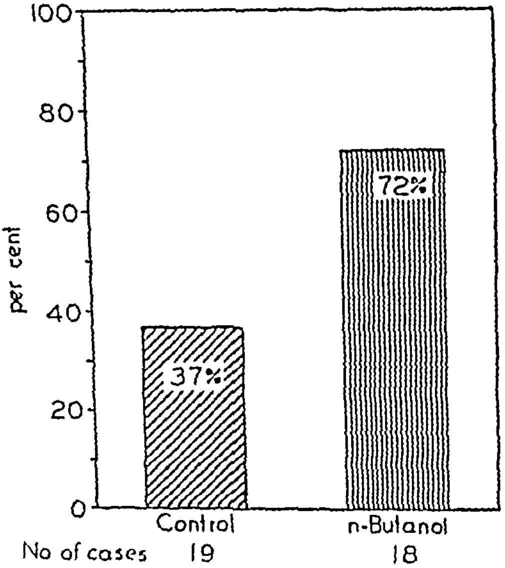


Fig 4 Wound healing as indicated by the percentage of cases having grossly and microscopically clear urine within 10 weeks after operation

The effect of n-butanol upon the degree of postoperative bleeding suggests that its action is not simply one of pain relief but is the result of more fundamental changes within the local wound process The exact nature of this action upon the degree of bleeding is not understood, but it does not appear to be a result of change in the coagulability of blood, nor of clot formation The ruddy complexion seen in these patients postoperatively would tend to indicate that it has a vasodilatory effect similar to ethyl alcohol It may be that n-butanol controls hemorrhage by restoring a normal chemical and physicochemical balance locally, thereby facilitating wound healing Studies in other types of hemorrhage have shown a similar hemostatic effect following parenteral administration

Wound healing The problem of wound healing was studied in these cases by bserving the length of time required for the urine to become crystal clear and terile, and for pus and red cells to disappear from the centrifuged specimens igure 4 illustrates the percentage of cases, observed for a sufficient period of ime, that had persistently clear urine, both grossly and microscopically, within ten weeks after operation

TABLE 2 *Surgical procedure*

CONTROL		N BUTANOL
10	Nephrectomy	10
3	Nephrolithotomy	2
5	Pyelolithotomy	4
4	Ureterolithotomy	2
3	Miscellaneous kidney or ureteral operations	7
25	Total	25

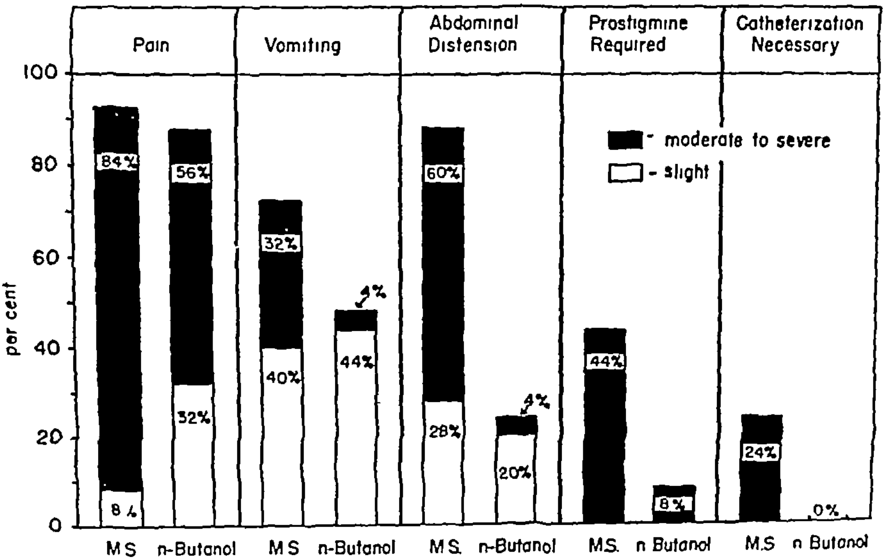


FIG 5 Complications following 50 kidney and ureteral operations

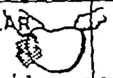
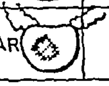
Among the control cases, 37 per cent, as compared with 72 per cent of the n-butanol treated cases, had clear urine within 10 weeks after operation The appearance of grossly and microscopically clear urine was considered to be the criterion of completed wound healing and re-epithelialization in the prostatic bed When this healing, for one reason or another, is delayed for long periods of time, ascending infection is the usual factor The improved rate of healing observed in the n-butanol treated group suggests again that n-butanol has a profound effect upon the local pathological process at the site of trauma

TABLE 9 *Incidence of metastases*

Age in Decades	Number of Patients	Per cent
40's	3	30 0
50	9	17 0
60	18	22 2
70	9	14 5
	39 Cases	

TABLE 10

TOTAL PERINEAL PROSTATECTOMY FOR CANCER OF THE PROSTATE PRIOR TO DECEMBER 31, 1950 *

EXTENT OF MALIGNANCY ON PREOPERATIVE EXAM	CASES	DIED WITH CANCER	DIED WITHOUT CANCER	SURVIVAL LIVING WITH CANCER	 LIVING WITHOUT CANCER
EXTRACAPSULAR & CAPSULAR 	38	12 (31 6%)	8 (21 1%)	4 (10 6 %)	14 (36 7%)
INTRACAPSULAR 	76	11 (14.5%)	23 (30 3%)	3 (3 9 %)	39 (51 3%)

*IN 17 OF THE EARLY CASES NO DEFINITE PREOPERATIVE RECTAL IMPRESSION WAS RECORDED AS TO WHETHER THE MALIGNANCY WAS INTRA OR EXTRACAPSULAR

SURVIVAL CORRELATED WITH ESTIMATED EXTENT OF MALIGNANCY ON RECTAL EXAMINATION RECORDED IN 114 PATIENTS

These cases are divided into A) intracapsular, 76 patients, and B) capsular or extracapsular, 38 patients

In 17 of the earlier cases no preoperative rectal impression was recorded as to whether the malignancy was intracapsular, capsular or extracapsular Thus only the remaining 114 of the 131 cases operated on prior to December 31, 1950 were divisible into these 2 groups The results are shown in table 10 Very few of the microscopic reports in the cases prior to 1950 referred to perineural lymphatic channel involvement as recently described by Hudson[10] which made it impossible to categorize the survival on this type of a classification

Clinical estimate Prostatic carcinoma, intracapsular on rectal examination a) Five-year survival Seventy-six patients were thought to have the cancer confined within the capsule on preoperative rectal examination, of these 14 subsequently had recurrence or metastases Of the remaining 62 patients, 39 were living or lived 5 years or more without evidence of recurrence or metastases, a 5-year survival rate of 63 per cent in these cases of early carcinoma (See table 1)

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[10] Hudson, P B , Finkle, A L and Totten, R Prostatic cancer Cancer, 5 1225-1228, 1952

b) Ten-year survival In these 76 patients with carcinoma confined within the capsule on rectal examination, 35 were operated on before December 31, 1945 and could be followed 10 years or more Twelve lived 10 years or more giving a 10-year survival of 34 per cent without evidence of recurrence or metastases The mean age in this group was 64 5 years (See table 2)

Survival by microscopic limit of the 76 cases clinically intracapsular a) Capsular or extracapsular by microscope The survival rate when carcinoma had spread locally beyond the clinical estimate revealed that out of 76 thought to be confined within the capsule on preoperative rectal examination, 34 showed either capsular invasion or extracapsular extension on microscopic examination Of these 34 cases, 15 (44 per cent) lived 5 years or more Twelve of these showed capsular invasion but no extension beyond the capsule of the prostate Eight of these 15 now have evidence of recurrence or metastases

b) Intracapsular by microscope Microscopic examination confirmed only 42 of the 76 to be actually intracapsular Thirty-two (76 1 per cent) patients of the 42 were living 5 years or more and 3 of them had evidence of recurrence or metastases Thirty-five patients in whom the rectal examination revealed that the growth was confined within the capsule clinically were followed 10 years or more Seventeen patients out of the 35 were confirmed to have microscopic intracapsular adenocarcinoma Eight of these lived 10 years or more, giving a survival rate of 47 per cent This figure approximates the expected survivorship of this age group in the general population A comparison of the clinical rectal impression and the postoperative microscopic findings follows

Location on Rectal	Cases	Microscopic Spread
Apex	10	4 confined 6 capsular or extracapsular
Base	9	5 confined 4 capsular or extracapsular
Lateral lobe	57	33 confined 24 capsular or extracapsular

The 10-year survival of patients with carcinoma based on microscopic extent was as follows

	Number of Patients With Surgery Before 1945	Microscopically Extracapsular	Microscopically Intracapsular
Rectal examination showed capsular and extracapsular extension	24	20 (5 lived 10 years or more = 25%)	4 (1 lived 10 years or more = 25%)
Intracapsular on rectal examination	35	18 (4 lived 10 years or more = 22 2%)	17 (8 lived 10 years or more = 47%

Clinical estimate Prostatic carcinoma, capsular or extracapsular on rectal examination a) Five-year survival In 38 patients who were thought to have capsular or extracapsular invasion on preoperative rectal examination, 22, followed 5 years or more, had no evidence of metastases and 14 (64 per cent) of these 22 lived 5 years or more Sixteen had recurrence or metastases and only 4 (25 per cent) of these lived 5 years or more In 11 of these patients the pathologist found

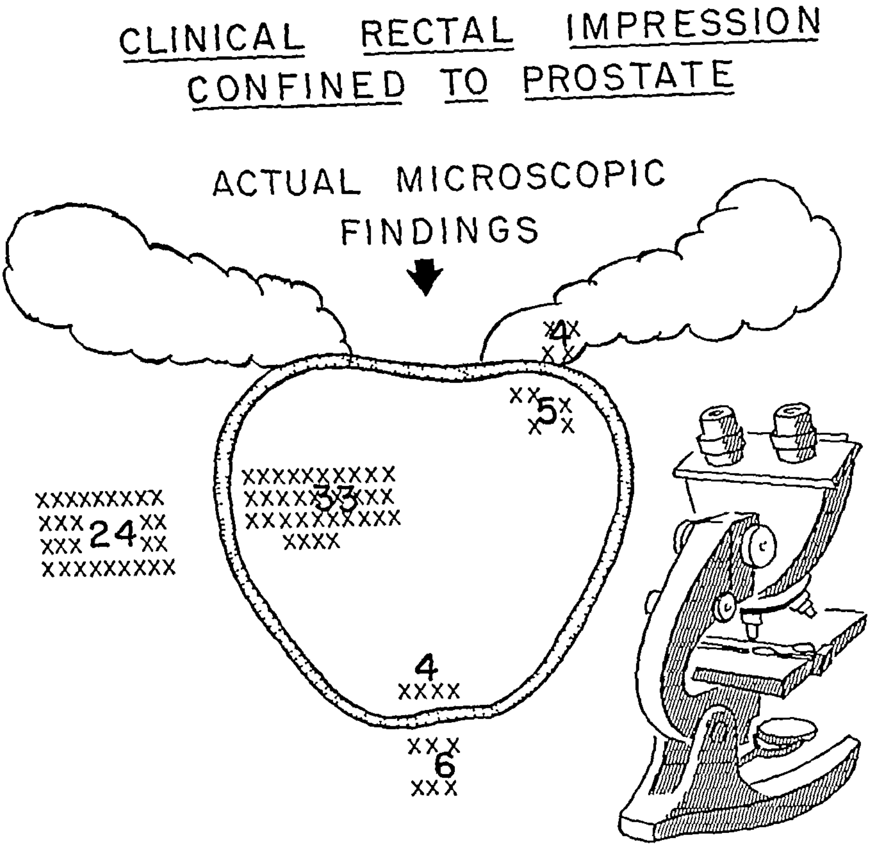

Fig 2

that the growth was within the prostatic capsule and a periprostatic inflammatory reaction had confused the clinical picture Seven of these lived 5 years or longer (table 10)

Microscopic Of the 27 microscopically confirmed to be capsular or extracapsular 11 (41 per cent) survived 5 years or more We feel that orchiectomy and estrogen therapy contributed to this survival period Rectal palpation as a clinical means of diagnosing malignancy of the prostate was found to be 84 per cent accurate in this series Rectal evaluation was less accurate than the microscopic evaluation revealed in determining the estimated extent or limit of the neoplasm (fig 2)

b) Ten-year survival Of the 38 cases with carcinoma thought to be capsular or extracapsular on rectal examination, 24 were operated on before December 31, 1945 Six (25 per cent) of these lived 10 years or longer (table 2)

INCONTINENCE

It is interesting to note that there was less overall incontinence in the group operated on prior to 1946 when a small (less than 1 cm) piece of the apex was left in place

In the 23 patients with temporary incontinence lasting less than 1 year, 14

TABLE 11 *Overall incontinence in 229 patients*

	Temporary Incontinence (4 months to 1 year)		Persisting Incontinence (more than 1 year)	
	Cases	Per Cent	Cases	Per Cent
1930–1945, 68 cases, less than 1 cm of apex left	5	7 4	2	2 9
1946–1955, 161 cases, complete prostate removed	18	11 2	12	7 5

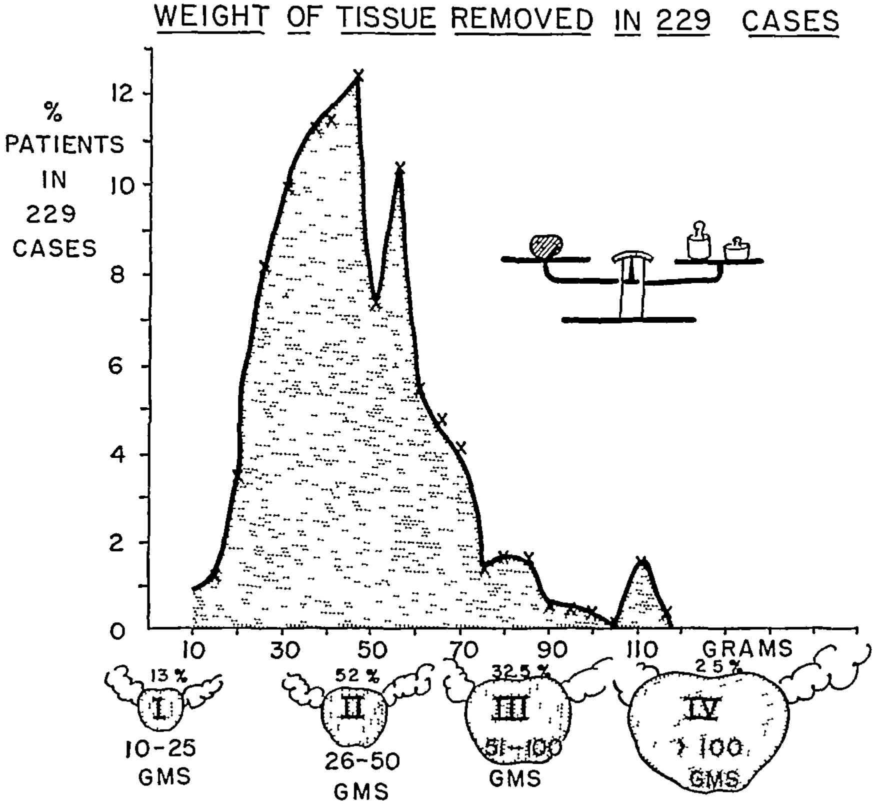

FIG 3

continued to have incontinence (table 11) The operative reports described most of these 14 earlier patients as having malignancy in the apical area involving the region of the external urinary sphincter In the less extensive growths incontinence was not a problem, but in these 14 the complete removal of the cancer traumatized the external urinary sphincter and in some cases excision of a portion of the sphincter was necessary to remove the growth completely

WEIGHT OF TISSUE REMOVED

In 229 patients 13 per cent had between 10 and 25 gm of tissue removed, 52 per cent had 26 to 50 gm excised at surgery, 32 5 per cent had 51 to 100 gm while 2 5 per cent had more than 100 gm of tissue removed See figure 3

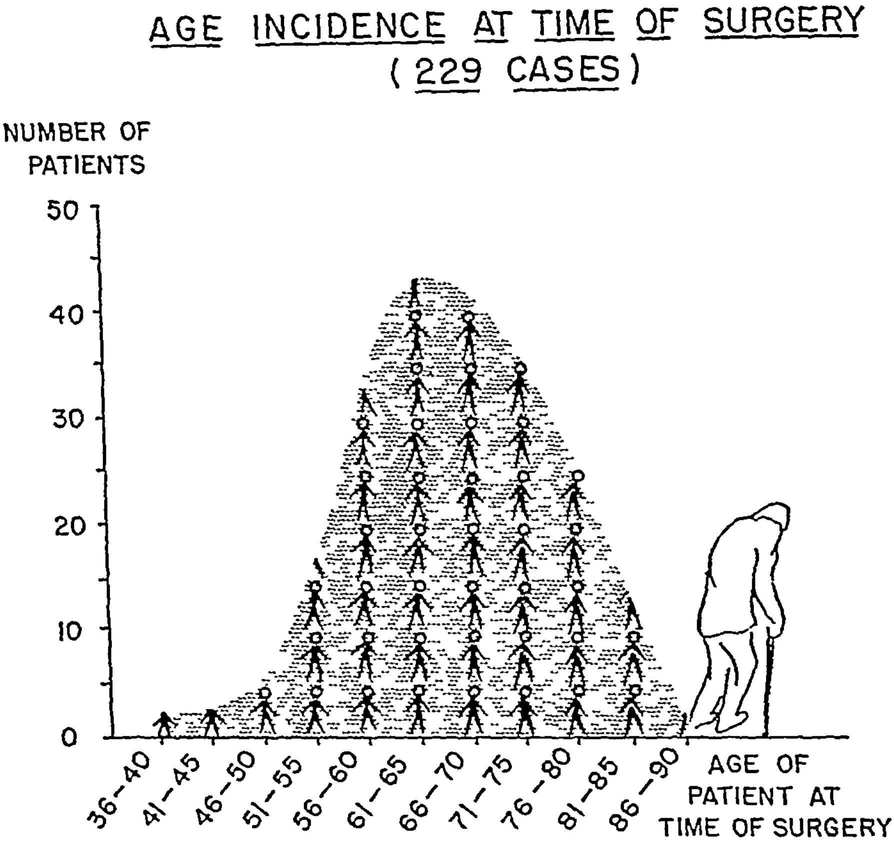

Fig 4

HOSPITALIZATION

The average hospital stay was 11 days over the 25-year period, but since the advent of antibiotics, and the modification of surgical technique, it is now approximately eight and one-half days.

AGE INCIDENCE AT TIME OF SURGERY

One hundred and fifty-six (68 per cent) patients were 60 years or older at the time of surgery (fig 4). Seventy-six (33.1 per cent) patients had reached the age of 70 or more before undergoing total perineal prostatectomy. The median age was 66 years. We feel that perineal prostatectomy subjects the patient to less shock than other methods of prostatectomy and that poor surgical risks tolerate this type of procedure with less morbidity.

RELATIONSHIP OF OPERATIVE AGE TO 5-YEAR SURVIVAL

The highest survival rate is found in the age group of 61 to 65 years (table 12). The 7.0 per cent survival in the age group of 46 to 50 indicates the severity of this disease in younger men.

TABLE 12 *Relationship of operative age to five-year survival in 131 patients*

Operative Age	Per Cent Surviving 5 Yrs or Longer
46–50	7 0%
51–55	10 5%
59–60	17 5%
61–65	22 8%
66–70	19 4%
71–75	14 0%
76–80	8 8%

PROSTATIC SURGERY EITHER BEFORE OR AFTER TOTAL PERINEAL PROSTATECTOMY

Previous prostatic surgery Fifty-five of the 229 patients had previous prostatic surgery Fifty-two had undergone transurethral resection of the prostate gland prior to total perineal prostatectomy Three patients had had a simple perineal prostatectomy first Radical removal of the prostate was more difficult in these cases[11]

Surgery following total perineal prostatectomy In 8 cases transurethral resection for obstruction at the bladder neck was necessary following total perineal prostatectomy

Interval Between Total Perineal Prostatectomy and Resection	Reason for the Transurethral Resection
2 years	Contracture of bladder neck
3 years	Recurrent carcinoma
5 years	Recurrent carcinoma
6 years	Suspected nodule which proved to be benign
7 years	Recurrent carcinoma
7 years	Recurrent carcinoma
8 years	Recurrent carcinoma
9 years	Recurrent carcinoma

LATENT MALIGNANCY—REVEALED AFTER SIMPLE PERINEAL PROSTATECTOMY

In a study of 1,694 cases of simple perineal prostatectomy,[12] a final pathological report of carcinoma was made in 81 patients Of these 81 patients, 24 were excluded from our study because, although it was known prior to operation that they had cancer of the prostate, a total prostatectomy could not be done Five additional cases were excluded as being done subsequent to 1950 Of the remaining 52 patients who underwent simple perineal prostatectomy in which latent carcinoma was revealed, 24 patients or 46 1 per cent lived or are living 5 years or longer Of the 36 patients operated upon prior to December 31, 1945, eight (22 2 per cent) lived or are living 10 years or longer The incidence of metastases for the 52 patients was 21 2 per cent The breakdown of this analysis is presented in table 13

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[11] Goodwin, W E Radical prostatectomy after previous prostatic surgery J A.M.A , 148 799–803, 1952

[12] Turner, R D and Belt, E Read at annual meeting, American Medical Association, Chicago, Ill , June 13, 1956, the results of 1,694 simple perineal prostatectomies

TABLE 13

Incidence of Metastases	5 Year Survival (52 Cases to 1950)	10 Year Survival (36 Cases to 1945)
11 with metastases (21.2%)	6 (11.5%)	1 (2 8%)
41 no metastases (78 8%)	18 (34 6%)	7 (19 4%)
52 (100 0%)	24 (46 1%)	8 (22.2%)

TABLE 14 *Postoperative complications in 229 cases*

	Patients	Per Cent
Temporary incontinence (4 to 12 months)	23	10 0
Persistent incontinence (more than 12 months)	14	6 3
Urethral stricture	9	4 0
Contracture bladder neck (only one had surgery)	7	3 1
Hemorrhage (four required evacuation of clots)	5	2 3
Breakdown of skin incision	4	1 7
Thrombophlebitis	4	1 7
Epididymitis	3	1 3
Pyelonephritis	3	1 3
Rectoperineal fistulas	3	1 3
Surgical ureteral obstruction	1	0 4
Calculus obstructing ureter during postoperative period	1	0 4
Perineal hematoma	0	0

SURVIVAL IN CASES OF SIMPLE PERINEAL PROSTATECTOMY ON MALIGNANT GLANDS

5-year survival The overall 5-year survival is 46 1 per cent

Age Group—Years	No of Patients	No. of Patients Surviving	Per Cent Surviving
50	7	4	57 1
60	18	11	61 1
70	22	9	39 1
80	5	0	0 0

10-year survival The overall 10-year survival is 22 5 per cent

Age Group—Years	No. of Patients	No. of Patients Surviving	Per Cent Surviving
50	3	2	66 7
60	16	5	31 3
70	13	1	7 6
80	4	0	0 0

COMPLICATION AT SURGERY IN 229 PATIENTS

Thirteen (5 7 per cent) patients required one or more transfusions during surgery One (0 4 per cent) patient had a recognized rectal perforation In this patient the operation followed the cancer through the involved rectal wall

POSTOPERATIVE COMPLICATIONS

Three rectoperineal fistulas developed after surgery on patients in whom the cancer was extracapsular (table 14) In one of these an anaplastic growth was

TABLE 15 *Early carcinoma of the prostate*

	No Patients Followed	5 Year Survival	10 Year Survival
		%	%
Palliative (Barnes)[7]	31	53	22
Radical (Jewett)[2]	78	61	37
Radical (Hinman)[8]	23	56 5	
Radical (Colby)[9]	34	55	
Total perineal (Belt) (rectally confined)	76	63	34
Total perineal (Belt) (microscopically confined)	53	68	43
Radical (Jewett)[2] (microscopically confined)	41		49

detected on microscopic examination In one the fistula developed because of a retained foreign body This was easily rectified by surgery 2 months later

COMPARATIVE SURVIVAL IN EARLY CARCINOMA

In his study of 31 cases definitely diagnosed as carcinoma of the prostate and considered to be within reach of total prostatectomy but instead were treated palliatively with estrogens, Barnes[7] noted a 5-year survival rate of 53 per cent and a 10-year survival rate of 22 per cent A study of table 15 shows the superiority of total perineal prostatectomy over estrogen therapy alone in this type of case

MISCELLANEOUS PATHOLOGICAL FINDINGS

Twelve patients were also treated for a known but unrelated malignancy in some other part of the genitourinary tract Three had adenocarcinoma of the prostate combined with tuberculosis of the prostate gland Two had a pathological (microscopic) diagnosis of sarcoma of the prostate One had a primary carcinoma of the seminal vesicle invading the prostate gland One had primary bladder tumor which invaded the prostate These two latter cases were excluded from the original 274 suspected carcinomas of the prostate which make up the substance of this report

Fifteen patients had deep x-ray therapy (before 1942) with a 6 8 per cent five-year survival Eleven of these fifteen died within five years Nine of the 11 patients had microscopic capsular or extracapsular invasion Only one of these patients lived 10 years and he had a microscopic intracapsular neoplasm

DISCUSSION

The value of any surgical procedure depends upon its enduring results It is well known that the memory is tricky in recalling its impressions, good impressions being retained much longer than the memory of failures and disasters

The labor of a statistical review of this type is justified by the fact that in such a study all factors are brought under scrutiny from the record written at the time This rules out the unreliability of memory and of emotional factors Judged by these hard statistical standards the procedure of total removal of the prostate for cancer is again shown to be valid

The method of study here presented has followed the principles so carefully laid down by Jewett[1,2] in two excellent presentations Comparison of his results with our own is thus quite easy The 229 patients here recorded closely follow in morbidity and mortality in course and complications those studied by Jewett

The central fact which emerges in his studies and in ours and which stands out clearly is that in those patients in whom the disease cancer of the prostate is recognized early and in whom the prostate with its cancer is removed before the cancer has gone beyond the prostatic capsule a 10-year survival rate is attained which closely approximates the survival rate of patients of this same age group in the general population This surgical feat is an accomplished fact

Therefore it follows that the need for the future lies in earlier recognition of this frequently occurring disease by the general practitioners of the community for as this study also shows simple digital examination of the posterior aspect of the prostate in the course of an ordinary rectal examination is a more effective means of discovering the presence of early cancer of the prostate than are more elaborate methods of study Hence if rectal examinations are routinely made in men of the age group in which cancer of the prostate may be expected to occur an effective surgical procedure total perineal prostatectomy is available for their cure

Total removal by urologists should be encouraged and promoted on the basis of the demonstrably higher survival rate associated with this form of surgical attack The good results obtained through its use in those patients in whom carcinoma of the prostate has been recognized early may be expected to greatly reduce the present dreadful mortality from this disease

SUMMARY

A 47 per cent 10-year survival rate after total perineal prostatectomy in that group of patients in whom the cancer of the prostate was microscopically confined to the prostate has been presented This is considered to be sufficient evidence to cause all urologists to be alerted to the need for the immediate application of this procedure for the cure of this disease

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WEGENER'S GRANULOMATOSIS: A CASE REPORT

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We have recently had a case of necrotizing granulomatosis with angiitis, also known as Wegener's granulomatosis. This is a rare disease, only 29 cases having been reported. It is a variant of polyarteritis nodosa and is probably due to a hypersensitivity reaction. It involves most commonly the respiratory tract, the kidneys, spleen and occasionally the liver and prostate. Fahey and Leonard[1] have described the clinical features of this disease in great detail. Usually, the presenting symptoms are due to upper respiratory tract inflammation as evidenced by nasal discharge, painful sinuses, sore throat, cough or hemoptysis, accompanied by signs of renal damage with albuminuria and red and white blood cells and casts in the urine. Terminally, the renal failure dominates the clinical picture. There may be symptoms due to a general arteritis shown by high fever, arthritis, muscle pain and widespread hemorrhagic lesions of the skin and mucous membrane.

In the case to be reported, the presenting symptoms were due to granulomatous inflammation in the prostate. The nature of the disease was not initially recognized. Since the biopsy of the prostate may furnish the first clue of this systemic disease, it is deemed worthy of bringing it to the attention of urologists.

CASE REPORT

E. M., a 63-year-old white male executive, was admitted to the hospital for the fourth time in 1954, because of inability to void urine. Acute retention had occurred 2 weeks prior to admission and recurred again 1 week prior to admission. A Foley catheter was inserted and he was admitted for definitive surgery.

Past history revealed that the patient had syphilis at age 24, for which he recieved intramuscular injections for 2 years. At age 46, a cholecystectomy was performed (first admission). His hospital course was uncomplicated, except for a mild albuminuria. He was readmitted 3 months later with acute pyelonephritis and a prostatic abscess. A lumbar puncture was normal as was a serological study of the spinal fluid. The same year he had some failure of vision which remained poor thereafter. Neurological examination revealed some paleness of the optic discs but was otherwise normal. A course of 15 intramuscular injections of tryparsamide was given (third admission). A lumbar puncture several months subsequent to therapy was also normal.

Physical examination in 1954 revealed a well-developed, well-nourished white man in no acute distress. The pupils reacted to light but only poorly to accommodation. The peripheral fields of vision were constricted. The mouth and pharynx were normal. The chest was clear and the heart was normal. The abdomen revealed a well-healed scar from previous surgery and mild diastasis recti

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[1] Fahey, J. L. and Leonard, Edward: Wegener's granulomatosis. Am. J. Med., 17: 168, 1954.

The prostate was smooth and markedly enlarged The remaining examination was not remarkable

Temperature, 98 6, pulse, 94, respirations, 20, blood pressure, 138/84

The hemoglobin was 13 8 gm per 100 cc, red blood count 4 35 million and white count 8,200 with 83 per cent polymorphonuclears, 15 per cent lymphocytes, 2 eosinophils Urea nitrogen was 9 mg per cent and the fasting glucose 93 mg per cent Blood Hinton was positive but the Wassermann was negative A chest x-ray showed slight prominence of the bronchovascular markings of the right lower lobe but was otherwise normal

On the third hospital day a suprapubic prostatectomy and bilateral vasectomy were performed The patient tolerated surgery well Following operation, pharyngitis and laryngitis developed with tender regional lymph nodes and inflamed vocal cords The temperature rose to 101 degrees on the fourth postoperative day, was then normal for 3 days, and again at levels up to 101 degrees for 3 days, thereafter normal The patient had been placed on dicrysticin postoperatively but this was changed to terramycin on the fourth postoperative day Despite antibiotics and local therapy, the pharynx remained red and sore His surgical wound healed well and he was discharged on the twenty-third hospital day, still complaining of a sore throat

Histopathologic examination of the prostatic tissue revealed benign prostatic hypertrophy and chronic granulomatous inflammation

The patient was hospitalized again, 1½ months later During the interval at home, the pharyngitis had persisted In addition, for several days prior to admission, he had been voiding cloudy urine almost hourly

Physical examination revealed the pharynx to be dry, red and glistening, with several small vesicles and superficial ulcerations It seemed distinctly worse than when seen 10 weeks earlier The physical examination was otherwise not remarkable

Temperature, 98 6, pulse, 100, respirations, 20, blood pressure, 140/90

The hemoglobin was 10 3 gm per 100 cc, red count 3 35 million and white count 11,950 with 74 per cent polymorphonuclears and 10 per cent bands Urinalysis showed a specific gravity of 1 017 with 2 plus proteinuria, and many white cells No casts were seen The blood glucose was 87 and the urea nitrogen 14 Urine cultures obtained by retrograde study grew out Aerobacter aerogenes and Pseudomonas aeruginosa A lumbar puncture was normal The Hinton and Wassermann tests were positive, the latter only weakly The acid phosphatase was 1 3 and the alkaline phosphatase 8 6 King-Armstrong units The thymol turbidity was 8 The total protein was 5 0 gm per cent and the albumin 1 0 gm per cent Smears and cultures of the urine sputum and spinal fluid were negative for tuberculosis X-ray of the chest revealed a dense, irregular shadow in the left apex behind the first rib A subsequent film 7 weeks later showed persistence of the lesion in the left apex prominent root structures on the left, and hazy infiltration in the posterior and central portions of the right lung interpreted as a focal area of pneumonitis A retrograde pyelogram was normal An L E cell preparation was negative and a calf-muscle biopsy showed chronic focal inflammation An electrocardiogram showed minor QRS changes, possibly consistent with some myocardial damage but not diagnostic Histopathologic examination following a transurethral resection again revealed focal granulomatous inflammation in the prostate

The patient's hospital course was slowly and progressively downhill He suffered generalized muscular pain, increased with movement In the fourth week, the urea nitrogen had risen to 39 and the creatinine was 1 4 In his sixth week in the hospital, and about one week prior to death, the blood urea nitrogen had risen to 135, creatinine, 6 3 The pharyngitis persisted Despite large doses of antibiotics, local and supportive therapy, he failed to respond The first 3 weeks of hospitalization were characterized by a febrile course with a maximum temperature of 103 8 With institution of cortisone by mouth, the temperature dropped to normal and remained so throughout the remainder of his hospitalization, although the heart rate was persistently rapid (100–120), and the white blood cell count mounted from 14,000 to 18,000 with 88 to 94 per cent polymorphonuclears The patient, however, did not otherwise respond With the onset of the elevated urea nitrogen to 187, his course was rapidly downhill He died on the fifty-first hospital day

The autopsy revealed the major pathological processes to be in the heart, lungs, kidneys, prostate, seminal vesicles, spleen, liver and adrenals There was interstitial myocarditis with infiltration by polymorphonuclear neutrophils and necrosis of muscle fibers and arteritis Periodic acid-Schiff stain was negative for micro-organisms

There was a generalized vasculitis chiefly involving the arterial tree with fibrinoid necrosis of the arterial walls and infiltration by polymorphonuclear neutrophils, histiocytes, and occasional foreign body giant cells and Langhans' cells In the lungs, prostate and seminal vesicles, there was a necrotizing granulomatous inflammation consisting of massive necrosis with surrounding aggregates of histiocytes and occasional foreign body giant cells and Langhans' cells Focal areas of necrosis were found in the liver, adrenals and lymph nodes In the kidneys, there was an exudative and proliferative glomerulonephritis with infiltration of the glomeruli by polymorphonuclear neutrophils and epithelial and endothelial proliferation of the glomeruli and capsular crescent formation Autopsy diagnosis Necrotizing granulomatosis with angiitis

DISCUSSION

Godman and Churg[7] have reviewed this peculiar disease complex and have noted that the triad of granulomatous inflammation with necrosis, angiitis and glomerulonephritis are the most common pathologic features in this disease These features were demonstrated in the case that is reported

The vascular lesion, although resembling polyarteritis nodosa, differs from it due to the presence of numerous histiocytes, as well as occasional foreign body giant cells and Langhans' cells Eosinophils may be present in variable numbers,

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Godman, Gabriel and Churg, Jacob Wegener's granulomatosis Pathology and review of the literature Arch Path , 58 533–553 1954 although none were found in the present case The glomerulonephritis was quite striking and appears to be another manifestation of a hypersensitivity reaction

One must consider the relationship of syphilis to this disease, since this patient had serologic evidence of syphilis The necrotic lesions with granulomatous inflammation differ from a gumma due to the absence of plasma cells, the more active acute inflammatory reaction that was present, as well as the vasculitis Furthermore, glomerulonephritis is more commonly seen in hypersensitivity states than in tertiary syphilis

As to the etiology of the hypersensitive reaction, the arsenical therapy may be a possibility However, this was given many years prior to the recent illness of the patient and it seems unlikely that this agent may have produced a reaction after such a long-time interval Therefore, the causative agent for the hypersensitivity state is not known

We have reviewed the initial surgical specimens of the prostate in this case and have confirmed the diagnosis of granulomatous inflammation There was noted a small area of necrosis but no evidence of vasculitis Granulomatous inflammation of the prostate is occasionally seen in surgically resected inflamed prostatic tissue Thus, Tanner and McDonald[3] found 34 out of 1028 inflammatory lesions of the prostate to be of granulomatous nature Usually, this granulomatous inflammation is of a nonspecific type We are of course excluding the cases of tuberculosis of the prostate which are seen so rarely now in the era of antibiotic therapy

Although granulomatous inflammations of the prostate may be nonspecific, one must consider the possibility of their being a peripheral manifestation of a generalized systemic disease The presence of vasculitis and necrosis should alert the examiner to this possibility The urologist who has a case of nonspecific granulomatous prostatitis must carefully evaluate the status of the upper respiratory tract and kidneys to rule out Wegener's granulomatosis or tuberculosis

The prognosis in this disease is poor Cortisone therapy has been suggested but this was to no avail in our case, possibly because of the far-advanced nature of the disease when this medication was first given

SUMMARY

A case is reported of necrotizing granulomatous angiitis, also known as Wegener's granulomatosis The patient initially had symptoms of urinary obstruction due to prostatic enlargement

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[3] Tanner F H and McDonald J R Granulomatous prostatitis Arch Path, 36 358, 1943

focal inflammation An electrocardiogram showed minor QRS changes, possibly consistent with some myocardial damage but not diagnostic Histopathologic examination following a transurethral resection again revealed focal granulomatous inflammation in the prostate

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[2] Godman, Gabriel and Churg, Jacob Wegener's granulomatosis Pathology and review of the literature Arch Path, 58 533–553, 1954

One must consider the relationship of syphilis to this disease, since this patient had serologic evidence of syphilis The necrotic lesions with granulomatous inflammation differ from a gumma due to the absence of plasma cells, the more active acute inflammatory reaction that was present, as well as the vasculitis Furthermore, glomerulonephritis is more commonly seen in hypersensitivity states than in tertiary syphilis

As to the etiology of the hypersensitive reaction, the arsenical therapy may be a possibility However, this was given many years prior to the recent illness of the patient and it seems unlikely that this agent may have produced a reaction after such a long-time interval Therefore, the causative agent for the hypersensitivity state is not known

We have reviewed the initial surgical specimens of the prostate in this case and have confirmed the diagnosis of granulomatous inflammation There was noted a small area of necrosis but no evidence of vasculitis Granulomatous inflammation of the prostate is occasionally seen in surgically resected inflamed prostatic tissue Thus, Tanner and McDonald[3] found 34 out of 1028 inflammatory lesions of the prostate to be of granulomatous nature Usually, this granulomatous inflammation is of a nonspecific type We are of course excluding the cases of tuberculosis of the prostate which are seen so rarely now in the era of antibiotic therapy

Although granulomatous inflammations of the prostate may be nonspecific, one must consider the possibility of their being a peripheral manifestation of a generalized systemic disease The presence of vasculitis and necrosis should alert the examiner to this possibility The urologist who has a case of nonspecific granulomatous prostatitis must carefully evaluate the status of the upper respiratory tract and kidneys to rule out Wegener's granulomatosis or tuberculosis

The prognosis in this disease is poor Cortisone therapy has been suggested but this was to no avail in our case, possibly because of the far-advanced nature of the disease when this medication was first given

SUMMARY

A case is reported of necrotizing granulomatous angiitis, also known as Wegener's granulomatosis The patient initially had symptoms of urinary obstruction due to prostatic enlargement

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[3] Tanner, F H and McDonald J R Granulomatous prostatitis Arch Path, 36 358, 1943

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RETROPERITONEAL LYMPHATIC CYST (CYSTIC LYMPHANGIOMA)

BENEDICT R. HARROW

From The Department of Urology, Mt. Sinai Hospital, Miami Beach, Fla.

Two recent papers[1, 2] stress the low incidence of mesenteric lymphatic cysts, but retroperitoneal lymphatic cysts are even more unusual. According to Pack and Tabah,[3] until 1954 approximately 870 primary retroperitoneal tumors of all types had been reported in the literature. From their references and those listed in this paper, I have estimated that approximately 70 retroperitoneal cysts have been recorded. Of these 70 cysts only 14 fit the criteria for the lymphatic variety. The following case satisfies all the requirements for the diagnosis of lymphatic retroperitoneal cyst.

CASE REPORT

Mrs. A. C. (hospital No. 35856) a 50-year-old white woman, was admitted to Mt. Sinai Hospital March 18, 1954. Three years before admission she had symptoms of acute cystitis which had responded rapidly to a sulfa drug. One month before admission another attack of acute bacterial cystitis subsided on oxytetracycline only to return again 1 week before admission to the hospital. At that time physical examination revealed a mass approximately 6 by 6 cm., freely movable, in the right midabdomen just lateral to the umbilicus. It did not feel unusually hard and was smooth, nonfluctuant, nonpulsating and moved with respirations. A plain film revealed an oval mass, 8 by 6 cm., overlying the psoas muscle shadow with its center just to the right of the fourth lumbar vertebra. An excretory urogram was taken March 12, 1954 using a mixture of 15 cc of 50 per cent neo-iopax and 15 cc of 35 per cent diodrast. With compression by a balsa block, the calyces, pelves and upper ureters were well demonstrated bilaterally and revealed a curling with a lateral deviation of the upper right ureter around the top of the mass with slight right hydronephrosis. An anteroposterior film taken immediately after release of compression in an upright position showed both lower ureters together with the rest of the deviation of the right ureter around the mass (fig. 1, *A*). A right oblique film (fig. 1, *B*) revealed clearly the entire outline of the tumor together with the upper ureter being markedly displaced anteriorly.

An x-ray of the chest was negative.

Past history was unimportant except for an appendectomy as a child and the removal of a fibroid tumor of the uterus 13 years previously.

On physical examination, besides the abdominal mass, a normal antiflexed uterus was palpated on pelvic examination with no adnexal masses. There were no generalized or localized lymph node enlargements.

Read at annual meeting, Southeastern Section of American Urological Association, Hollywood Beach, Fla., March 25-29, 1956.

[1] Konski, J. G.: Mesenteric chylangioma. Am. J. Surg., 87: 891-897, 1954.

[2] Miller, D. B.: Chyle cyst of the mesentery. Arch. Surg., 68: 359-363, 1954.

[3] Pack, G. T. and Tabah, E. J.: Primary retroperitoneal tumors. A study of 120 cases. Internat. Abs. of Surg., 99: 209-231, 313-341, 1954.

Laboratory data Hemoglobin 12 3 gm , red blood cells 4 5 M , white blood cells 6,000 with normal differential Urinalysis Albumin 0, sugar 0, specific gravity, 1 021, microscopic, 3–6 white blood cells per high power field

At operation, March 19, 1954, a right transverse, oblique incision was made extending from the lateral border of the rectus muscle below the umbilicus toward the twelfth rib in order to avoid severing segmental nerve trunks A yellow, oval tumor was located extraperitoneally on the psoas muscle adjacent to the third, fourth and fifth lumbar vertebrae The tumor was easily freed from the ureter and surrounding tissues It was adherent to the inferior vena cava, the bifurcation of the aorta, and the right common iliac artery but only by loose areolar tissue It was easily dissected free without bleeding The lesion was removed intact but on incising the last connection near the vertebral column a small amount of chylous fluid escaped although no opening had been made in the tumor itself This chylous fluid probably escaped from communicating channels with the abdominal lymphatics

The gross specimen consisted of an oval, yellow mass measuring 8 by 7 cm This specimen, when opened, was found to be a cyst filled with chylous or milky fluid The wall itself was thin and soft in some areas while other portions were semifirm and thicker A trabecular pattern of ridges was present on the inner surface The wall of the cyst was thick and consisted mainly of fibrous tissue (fig 2) A large amount of lymphoid tissue consisting of lymphocytes was present as thick collections in the walls and also just outside the walls of the cyst in the surrounding areolar tissue There were also numerous small lymph nodes

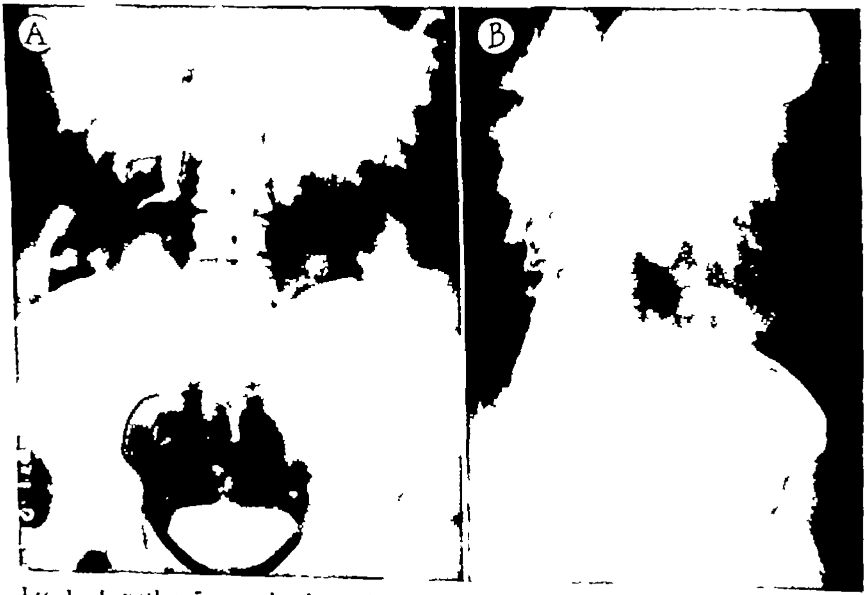

FIG 1 A, within 5 seconds after release of compression in upright position notice that calyces and pelvis have emptied partially Lower ureters are visualized with rest of deviation of upper right ureter depicted B, re application of compression with oblique placement and taking of rapid x ray demonstrate clearly anterior displacement of right ureter

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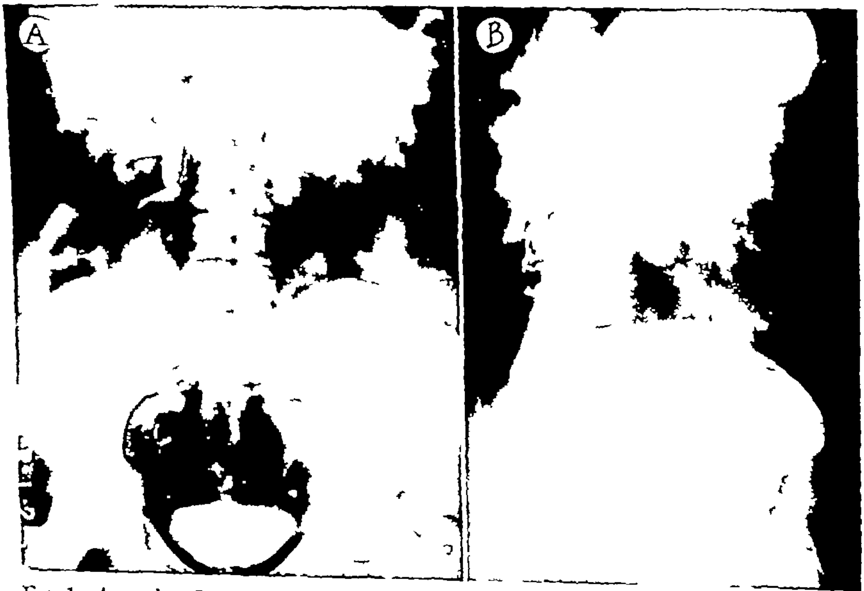

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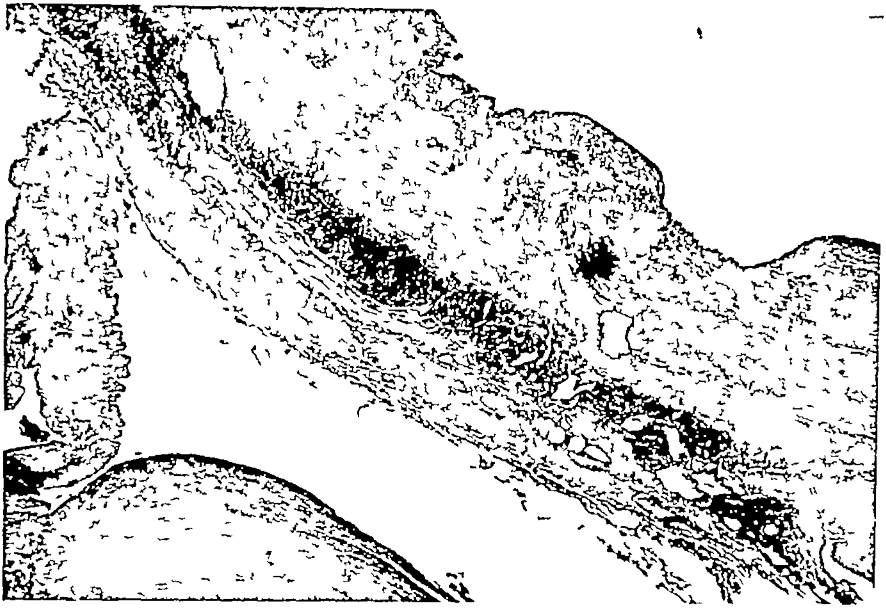

FIG 2 Upper section shows thickened area of wall while lower section discloses a thin portion Top represents inner surface of cyst wall Note thick fibrous portion, lymphatic tissue, numerous lymph spaces and areolar outer surface

on the outer surface of the wall The wall itself included numerous empty spaces of lymph channels which were lined by thin endothelial cells The inner lining was composed of endothelial cells with no cuboidal or columnar cells apparent

Diagnosis Typical lymphatic cyst (chylangioma cysticum) of the retroperitoneal space

Convalescence was uneventful and a checkup examination 1 year later revealed an asymptomatic patient whose physical examination and urinalysis were negative

COMMENT

There are three kinds of lymphangiomas simple, cavernous, cystic The simple form represents a new growth of small lymphatic channels lined with endothelium, similar to angioma but containing no blood The cavernous type consists of communicating lymph-filled locules separated by septa The third form consists of cysts which may be uni- or multilocular It is evident that the cystic type could arise from cavernous forms in which one compartment enlarges breaking septa and compressing other compartments Most authors are agreed that the lymphatic cysts, which are also known as cystic chylangiomas or lymphangiomas, should contain most of four identifying elements to differentiate them from other type cysts 1) The lining of the cyst should be endothelial (or absent) and must not be cuboidal or columnar epithelium 2) Small lymphatic spaces, numerous in some areas, should be found in the wall 3) Lymphoid tissue should be fairly abundant in the wall as diffuse collections of lymphocytes or as configurations similar to true lymph nodes 4) Foam cells containing lipoids exist in varying numbers

Surprisingly the chylous or milky fluid is not a necessary component for the diagnostic picture Usually chylous fluid is contained but actually hemorrhagic and occasionally only serous or straw colored fluid may be present In other words diagnosis is derived from the microscopic pathology Analysis of the chylous fluid is of little value has been done in few cases and reveals varying amounts of protein and lipoid material Messer[3] reviewed the results of several investigators comparing also chylous effusions with the fluid from these tumors A variation in the contents of the cysts can be explained by different degrees of stasis which in turn is influenced by the number of communicating channels with the abdominal lymphatics These communications are always present but often to only a slight degree X-ray evidence of channels has never been obtained in abdominal lymphatic cysts but has been from chylangiomas of the thorax[6] In this case report the escape of chylous fluid while dissecting the last point of attachment to the vertebral column yet without opening the cyst probably indicated the location of the communications It would be interesting to prove such communicating channels by giving the patient Sudan 3 100 mg in butter for several days before operation[7] Such a demonstration has been attempted only once unsuccessfully in one patient in whom the cyst was marsupialized

The benign simple lymphangiomas have not been found in the retroperitoneal space although 2 cases of malignant lymphangio-endotheliomas have been presented[4] One cavernous lymphangioma was mentioned by Donnelly[5] All other benign lymphatic tumors of the retroperitoneal space have been of the cystic type Kretschmer and Hibbs[3] in their review of the literature up to 1934 found only 5 cases of true lymphatic cysts including their own patient Ingraham and Nelson[1] reported another in 1939 and believed that a case of Swick should also be included bringing the total to 7 Gerster[11] also in 1939 presented a true cystic lymphangioma Since then there were those of Lee[12] Nichols[13] Beahrs et al[4] and Lingenfelter and Howard[4] Most recently Simon[15] presented

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[4] Beahrs O H Judd E S and Dockerty M G Chylous cysts of the abdomen Surg Clin N A 30 1081–1086 1950

[3] Messer F C Analysis of fluid from a chylous mesenteric cyst J Lab & Clin Med 23 595–601 1938

[4] Lowman P M Waters L L and Stanley H W Mesenteric chylous cysts J Internal Coll of Surg 18 265–270 1952

Johnston D W Chyluria Case report and review of literature Ann Int Med 42 931–937 1955

Donnelly B Primary retroperitoneal tumors Surg Gynec & Obst 83 705–717 1946

[3] Kretschmer H and Hibbs W Retroperitoneal perirenal lymphangioma Arch Surg 29 113–125 1934

Ingraham C B and Nelson J M Retroperitoneal cystic lymphangioma Am J Obst & Gynec 37 251–257 1939

Gerster J Retroperitoneal chyle cysts Ann Surg 110 389–410 1939

Lee F C Large retroperitoneal chylous cyst Arch Surg 44 61–71 1942

Nichols M H Retroperitoneal cysts Ann Surg 126 330–340 1947

[4] Lingenfelter F and Howard P Retroperitoneal tumors Am Surg 17 632–637 1951

[3] Simon H E Retroperitoneal chylous cysts Am J Surg 91 372–376 1956

2 cases which were called lymphangiomas and fulfilled most of the microscopic criteria

It is noted that Gerster, in a discussion of his paper, stated he had found about 16 to 18 lymphatic retroperitoneal cysts in a complete review of the literature However, he included reports such as that of Strauss and Sayre[16] where there was no microscopic report of the cyst wall Other such case histories, not accepted by most authors because of the perfunctory records, were those of Hadley,[17] Barney,[18] Brady,[19] Berger and Rothenberg,[20] and Nordland and Nordland [21] Carter et al [22] reported a calcified, retroperitoneal, multilocular cyst named as a chylangioma but it only contained a calcified fibrous wall Microscopically, the diagnosis of lymphatic cyst was not substantiated Chylous fluid alone does not justify the diagnosis since such fluid may result from fatty degeneration, old hemorrhagic degeneration, or diffusion into the cyst It is possible that these cysts which contain a fibrous wall with an endothelial layer but lacking lymph channels and lymphoid tissue might represent lymphatic cysts which have been modified because of high intracystic pressure, necrosis or hemorrhage This reasoning applies particularly to the multilocular forms which are considered similar to hygromas It is equally plausible that the origin occurred from the urogenital apparatus, only modified by the same factors Even if such cases are included only about 30 lymphatic cysts will have been reported in the English literature If the classification and etiology of these cysts are to be clarified, more careful and complete pathological data should be gathered with multiple sections from various portions of the wall

Scholl[23] discussed the cases of 2 patients with peripelvic lymphatic cysts of the kidney These are not considered to be retroperitoneal since by definition primary retroperitoneal tumors are those not contiguous with other organs such as pancreas, colon, adrenals or kidneys The diagnosis of these 2 cases as lymphatic cysts is even doubtful since the microscopic description included only the endothelial layer and not the lymph sinuses, lymphoid tissue or lipoid cells

Chylous mesenteric cysts are identical tumors with those in the retroperitoneal area The single difference is in location with only the retroperitoneal type being in the urological specialty Approximately 600 mesenteric cysts have been reported with details on only 200 and with the number of true lymphatic types indeterminate because of incomplete reports [4 6 24] Typical cystic lymphangiomas also occur in the omentum[25] Theories on the origin of the mesenteric and retroperitoneal chylangiomas have been discussed by numerous authors listed in the references and will not be reviewed in this paper The most logical and simple explanation is that of a developmental defect in the lymphatic anlage of the abdomen

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[16] Strauss, S F and Sayre, B E Retroperitoneal chyle cyst Ann Surg , **102** 1118, 1935

[17] Hadley, M The origin of retroperitoneal cystic tumors Surg , Gynec & Obst , **22** 174–175, 1916

[18] Barney, J D A case of retroperitoneal cyst Boston Med & Surg J , **193** 908–911, 1925

[19] Brady, L A further study of extraperitoneal pelvic conditions in women Am J Obst & Gyn , **32** 577–592, 1936

[20] Berger, L and Rothenberg, R Cysts of the omentum, mesentery and retroperitoneum Surgery, **5** 522–534, 1939

[21] Nordland, M and Nordland, M A Retroperitoneal cysts and tumors J Internat Coll Surg , **16** 731–739, 1951

[22] Carter, R E , Cholnoky, T de and Markman H D Retroperitoneal multilocular chylangioma cyst with calcification Am J Surg **52** 338–345 1941

[23] Scholl, A J Peripelvic lymphatic cysts of the kidney J A M A , **136** 4–7, 1948

[24] Burnett W F , Rosemand, G P and Bucher, R M Mesenteric cysts Arch Surg **60** 699–706, 1950

Other types of retroperitoneal cysts are assumed to result from embryological defects in the urogenital apparatus arising from such structures as the wolffian body (mesonephros), wolffian duct, müllerian duct or germinal epithelium Such types are illustrated by Greene,[26] Lahey and Eckerson,[27] and Hinman et al[28] Other rare types of retroperitoneal cysts said to occasionally occur are traumatic, parasitic (Echinococcus), dermoid or teratoid and tuberculous[6]

SYMPTOMS, DIAGNOSIS AND OPERATION

Retroperitoneal cysts are frequently asymptomatic and are discovered only because of a palpable abdominal mass Patients with symptoms usually complain of vague, nonlocalized abdominal pain Rarely, complaints such as nausea vomiting, diarrhea, leg pain and leg edema arise from pressure on the intestines, nerve trunks, or large abdominal blood vessels Renal pain from hydronephrosis is most unusual Recurrent cystitis in the present case report was probably coincidental Cystitis, however, did bring the patient to the physician so that the mass could be palpated

Retroperitoneal tumors represent an overlapping territory for urologists, surgeons and, occasionally, gynecologists The aid of roentgenologists for gastrointestinal studies, gastroenterologists, endocrinologists and hematologists may be elicited[29] The urologists contribute importantly to the diagnosis because of displacement of urinary tract structures Anterior (ventral) displacement of the ureter as occurred in the patient under discussion, or the kidney, is conclusive evidence of a retroperitoneal lesion[29] Lateral displacement occurs with both intra- and retroperitoneal growths Medial distortion of the kidney or ureter is presumptive evidence of a retroperitoneal tumor since most intraperitoneal space-producing lesions, particularly the lower abdominal ones, push the urinary tract laterally However, it must be realized that certain intraperitoneal expansions such as from enlarged livers, spleens, or gallbladders, occasionally move the kidney and ureter medially[30-32] Posterior (dorsal) movement of the ureter is limited by muscular structure

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[25] Beahrs O H and Dockerty, M G Primary omental cysts of clinical importance Surg Clin N A 30 1073–1079, 1950

[26] Greene, L F Extreme renal displacement due to retroperitoneal tumors J Urol, 59 174–178, 1948

[27] Lahey, F and Eckerson E Retroperitoneal cysts Ann Surg, 100 231–237, 1934

[28] Hinman F Gibson, T and Kutzmann, A Cysts of the wolffian body Ann Surg, 79 762–769, 1924

[29] Brodny M L and Hershman, H The enigma of retroperitoneal masses J Internat Coll Surg 18 469–478, 1952

[30] Weyrauch H M The significance of renal torsion in the diagnosis of retroperitoneal tumors Use of the lateral pyelogram J Urol 41 877–892 1939

[31] Coplan, M J Woods F M and Melvin, P D Abdominal tumors—a urological perspective Am Surg 17 1160–1167 1951

[32] Schulte T L and Emmett, J L Urography in the differential diagnosis of retroperitoneal tumors J Urol, 42 215–219 1939

In my patient the diagnosis of location was proved solely by excretory urography By taking x-rays within seconds after releasing compression in an upright position, both anteroposterior and oblique films visualized the ventrolateral ureteral deviation Adequate and proper use of compression (for only 2 minutes if used correctly, by tightening the band every few seconds since it loosens with each respiration) is invaluable in acquiring x-rays of retrograde quality in a high percentage of excretory urograms [33, 35] Nevertheless, retrograde urograms will often be necessary Other diagnostic tools such as presacral gas injection, pneumoperitoneum and laminography can be utilized but have been of limited value Occasional morbidity and mortality have occurred after presacral injections because of embolism and infection [35, 37] Aortography[38] and abdominal venography[39] occasionally may be used to advantage in selected instances Except for laminography, combinations of these procedures, although producing striking pictures, have generally been abandoned because of expense, risk and lack of value [37]

In handling the problem of a retroperitoneal tumor the urologist should be familiar with the various aspects of pheochromocytomas and adrenal tumors Generalized lymphomas such as leukemia, Hodgkin's disease or lymphosarcomas should be ruled out by lymph node biopsy if enlarged nodes exist, complete blood count, or bone marrow studies Occasionally a lymphoma is localized to the abdomen but in this instance operation is indicated for diagnosis even though the lesion can rarely be removed in toto [3, 40] A careful examination of the scrotum is mandatory since large retroperitoneal masses may be produced by metastasis from barely palpable testicular neoplasms [31] A careful pelvic examination in women is necessary since small ovarian, uterine or cervical carcinomas can produce the same type of retroperitoneal metastases

Butler and Bargen[41] found that mobility, tenderness and shape of the mass were of little value in differentiating between benign and malignant abdominal lesions Therefore, the urologist must be prepared for encountering sarcomas that require extensive procedures utilizing generous incisions if they are to be adequately removed Even benign appearing, fatty tumors, a total of 300 having been reported, have been found to be frequently sarcomatous,[42] and thus require careful and complete excision An oblique, transverse, extraperitoneal approach

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[33] Harrow, B R Intravenous urography using mixtures of radiopaque agents Radiology, 65 265–270, 1955

[34] Harrow, B R Experiences in intravenous urography using hypaque Am J Roentgenol 75 870–876, 1956

[35] Harrow, B R Simplified method for evaluation of left suprarenal and gastric masses J Florida M A, 42 732–734, 1956

[36] Steinbach, H L and Smith, D R Extraperitoneal pneumography in diagnosis of retroperitoneal tumors Arch Surg, 70 161–172, 1955

[37] Evans, A T Combined use of contrast media in retroperitoneal tumors Arch Surg, 70 191–198, 1955

[38] Berry, J F, Robbins, J J and Pirkey, E L Abdominal aortography Arch Surg, 70 173–177, 1955

[39] Kaufman, J J, Burke, D E and Goodwin, W E Abdominal venography in urological diagnosis J Urol, 75 160–168, 1956

[40] Butler, D B and Bargen, J A Abdominal masses, I A survey of their incidence and clinical significance Gastroenterology, 19 1–12, 1951

[41] Butler, D B and Bargen, J A Abdominal masses, V Systemic diseases and diseases of special regions Gastroenterology, 19 303–319, 1951

[42] Farbman, A A Retroperitoneal fatty tumors Arch Surg, 60 343–362, 1950

carries less morbidity than the transperitoneal procedure,[43] nevertheless, the peritoneum should be opened when better exposure is required Preoperative preparation of the colon for possible resection and special vascular clamps for the aorta and vena cava should be considered In rare instances arterial grafts may be required [44] Sometimes cysts can be so large and adherent to surrounding tissues that marsupialization has been used [4, 45] This procedure should rarely be necessary except in unusual circumstances [15]

SUMMARY

A retroperitoneal lymphatic cyst (cystic lymphangioma) is reported, bringing the total number in the English literature to 15 Their relationship to mesenteric, omental and other types of retroperitoneal cysts is presented This paper stresses that the diagnosis of a lymphatic cyst depends mainly upon the cyst wall histology rather than the mere presence of chylous fluid The urologist's participation in diagnosing and treating retroperitoneal tumors has been briefly reviewed

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[44] Tidrick, R T and Goldstein, M S Surgical treatment of retroperitoneal tumors Arch Surg , 70 203-206, 1955

[45] Slocum, M A Surgical treatment of chylous mesenteric cyst by marsupialization Am J Surg , 41 464-473, 1938

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TRAUMATIC URINARY INJURIES PITFALLS IN THEIR DIAGNOSIS AND TREATMENT

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Interest in improved management of the urinary tract has developed during the last 20 years in reports in the literature by urologists of results in their own observed series of cases of trauma and of suggestions for some standardization of the management of such cases Representative reports are the papers of Wood,[1] Prather,[2] Sargent,[3] [4] Lowsley and Menning,[5] Lewis,[6] Orkin,[7] Kimbrough and Furst[8] and McKay, Baird and Lynch [9] [10]

While there has been agreement concerning the diagnosis and treatment of the ruptured urethra and bladder as proposed by Lewis,[6] there has been a divergence of opinion as to the proper management of the injured kidney as noted by Braasch and Emmett [11] At one extreme has been the recommended surgical exploration of injured kidneys evidencing gross hematuria,[5] and at the other extreme has been the attitude of many urologists that watchful waiting is to be preferred and surgical intervention resorted to only in case of clinical deterioration or complications, whether early or late

Between these widely separated points of view fall the opinions of several clinical investigators who have attempted, by analysis of their own cases, in some way to more definitively diagnose the degree of injury to the kidney and to set forth certain criteria for the management of renal injury Sargent[3] [4] and McKay and his associates[10] have proposed classifications of the degree of renal injury predicated on the findings by retrograde pyelography, which was generally not in use prior to these reports because of the postulated danger of introducing infection or of inciting further hemorrhage Probably more generally accepted was the recommendation of Sargent[4] for observation in those cases where the pyelogram "is reasonably intact" and exploration in those patients showing greater disintegration of the kidney on pyelography Feeling this classification to be vague and not truly definitive, McKay and his associates[10] proposed a classification which places all injuries of the kidney in three groups

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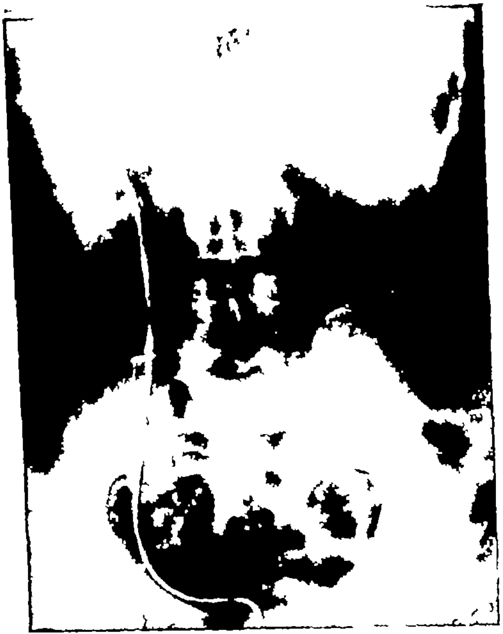

FIG 1 Post traumatic perirenal cyst, anterior projection Case of Colston and Baker

Group 1 includes patients with intact pyelograms and clear renal and psoas shadows, and not requiring exploration, group 2 includes patients with any rupture of the renal collecting system or loss of renal and psoas shadows, these to be explored in 72 hours, and group 3, those patients in unresponsive or recurring shock due to rupture of the renal vascular pedicle, these to be operated on as an immediate life-saving procedure It is of interest that Kimbrough and Furst[8] vary only in the exploration of group 2 patients in 24 to 48 hours rather than in 72 hours, the purpose of delay in either case being to allow thrombosis of ruptured vessels, permitting inspection of the kidney at the time of exploration and to allow the delineation of infarcts, thus allowing the operator a more adequate opportunity to judge whether the kidney should be salvaged or removed

Hodges, Gilbert and Scott[12] have recommended exploration in borderline patients, having noted the development of deleterious sequellae in a high percentage of ruptured kidneys which were not drained surgically Colston and Baker[13] have reported the occurrence of calcified perirenal cysts in a number of such patients (fig 1) Lynch and Large[14] have observed the occurrence of renal atrophy due to ischemic infarction in patients assumed to have contusion of the kidney and Arnold, Goodwin and Colston[15] have reported hypertension developing in similar patients

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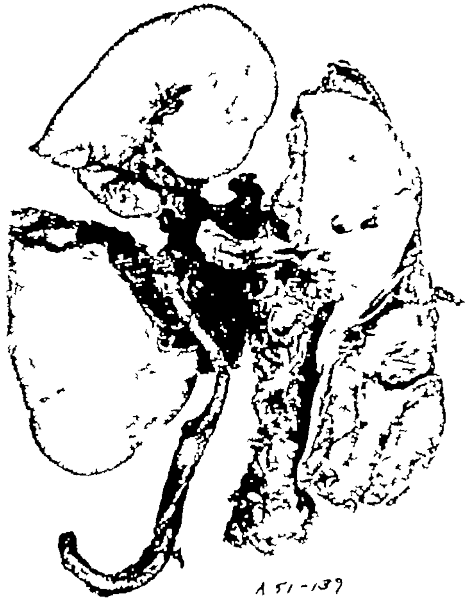

FIG 2 Case 1 Autopsy specimen showing complete rupture of renal artery

With this background review, it is the purpose of our paper to present certain case histories illustrating some of the pitfalls in the management of urinary injuries, and to suggest or emphasize certain "rules of thumb" for their diagnosis and treatment

CASE REPORTS

Case 1 L W , a 35-year-old white woman, was admitted to the hospital on the surgical service with pain in the left flank and abdomen following an automobile accident Shock, which was present when she was seen in the emergency room, responded to transfusion with whole blood, and a laparotomy was performed with the presumptive diagnosis of rupture of the spleen because of rigidity and a palpable mass in the left upper quadrant of the abdomen The spleen was found to be intact and a large retroperitoneal hematoma in the region of the left kidney was discovered but not opened Urinalysis was performed following the operation and grossly bloody urine was discovered, urological consultation was requested 10 hours later When examined, the patient was in profound shock which did not respond to multiple transfusions of whole blood, she was anuric and a portable film of the abdomen showed obliteration of the left renal and psoas shadows The patient expired in shock Autopsy examination demonstrated bisection of the left kidney with complete rupture of the renal artery (fig 2) and a retroperitoneal hematoma estimated to contain 3,000 cc of blood, the liver showed ischemic infarction due to the prolonged period of shock with ischemia of the viscera

Comment This patient presented a typical group 3 renal injury as described by McKay and his associates[10] Urinalysis and a portable x-ray film of the abdomen in the emergency room should have led to immediate urological consulta

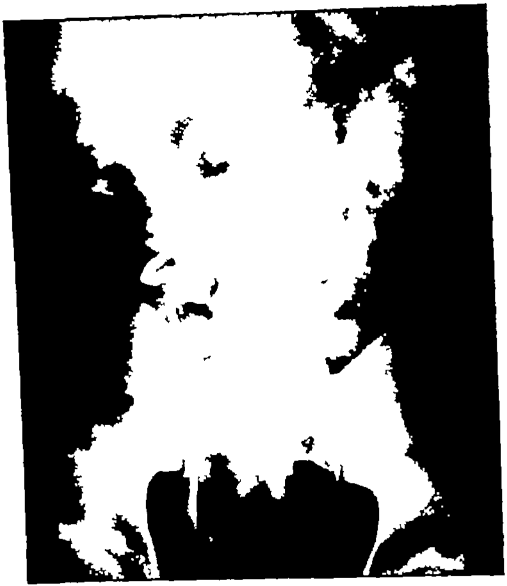

Fig 3 Case 2 Retrograde ureterogram showing extravasation of dye in fistula

tion, the diagnosis of rupture of the renal pedicle when the patient subsided back into shock after the initial favorable response to transfusion and emergency nephrectomy with ligation of the ruptured pedicle

Case 2 W J , a 42-year-old white man, was admitted to the hospital on the surgical service following an automobile accident He was found to have pain, abrasions, tenderness and a palpable mass in the right flank and right upper quadrant of the abdomen The patient was in shock which responded to transfusion with whole blood An x-ray of the abdomen showed absent right renal and psoas shadows and a normal left renal shadow and psoas shadow Operation was performed 6 hours later with the diagnosis of rupture of the right kidney A transperitoneal approach was elected and a large retroperitoneal hematoma in the region of the right kidney was opened, loose fragments of kidney removed and the pedicle clamped blindly because of severe active bleeding A stab wound made retroperitoneally in the flank subsequently drained urine An intravenous urogram showed function from the remaining superior pole of the kidney A retrograde ureterogram showed extravasation of the medium through the cutaneous fistula (fig 3) Secondary operation was required to remove the residual secretory kidney

Comment This patient had responded to shock therapy and was not in need of an emergency operation as a life-saving procedure Delay of the operation for 72 hours would probably have allowed thrombosis of the ruptured vessels, thus allowing adequate visualization for removal of the entire kidney A lumbar approach may have afforded more adequate control of the renal pedicle and removal of all portions of the fragmented kidney

Case 3 D H , a 58-year-old white man, was admitted to the hospital on the urological service with alcoholic intoxication and severe abdominal pain after having fallen in his bath tub He was unable to urinate and a catheter inserted

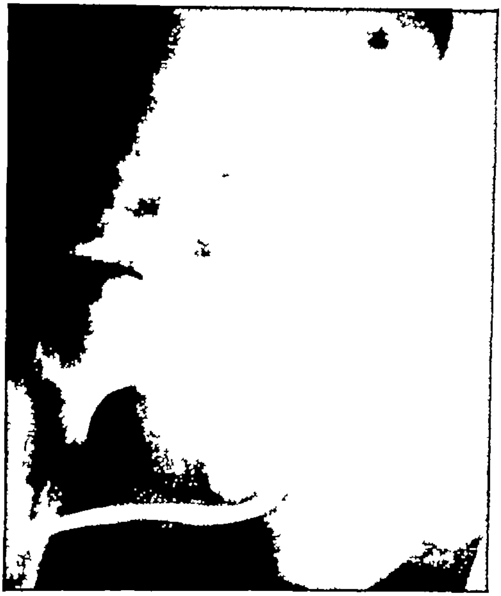

FIG 4 Case 4 Urethrogram showing perineal fistula

per urethram into the bladder recovered 150 cc grossly bloody urine An excretory urogram showed normal upper tracts and a normal bladder outlined by the excreted medium The resident's impression was that the patient had a contusion of the urinary tract of undetermined site When seen by the attending urologist 6 hours later, the patient had not urinated since removal of the urethral catheter and the abdomen was rigid A retrograde cystogram showed intraperitoneal extravasation of the medium and loops of intestine in the vertex of the bladder Surgical repair was performed and the patient recovered uneventfully

Comment Loops of intestine may partially seal an intraperitoneal rupture of the bladder and prevent extravasation of the medium on excretory urography The diagnosis of rupture of the bladder should be made or ruled out by retrograde opaque cystography using sufficient fluid to distend the bladder

Case 4 J A C , a 10-year-old white boy, was run over by a school bus and admitted to his local hospital on the surgical service where compound leg fractures and a fracture of the symphysis pubis were diagnosed by x-ray The leg fractures were submitted to open reduction He failed to urinate postoperatively and was found to have a distended bladder some 18 hours later A urethral catheter could not be passed and a suprapubic cystostomy was performed without attempted urethral catheterization, although the bladder was found to be intact The suprapubic catheter was removed several weeks later, the patient was unable to urinate and drained urine through the cystostomy sinus An abscess developed in the perineum, ruptured through the skin in the left gluteal fold and formed a second urinary fistula When seen in urological consultation several months later, x-ray examination revealed a bladder calculus, and the described suprapubic and perineal fistulas (fig 4)

Comment Fracture of the symphysis pubis and failure to pass a urethral catheter should have made the correct diagnosis of rupture of the membranous urethra rather than the bladder and continuity of the urethra should have been established at the time of operation with complete recovery of urinary function except for the possibility of a stricture at the site of rupture

DISCUSSION AND CONCLUSIONS

Definitive diagnosis should be made of the location and severity of injury to the urinary tract This is suggested in renal injury by the plain x-ray film showing loss of renal and psoas shadows and by the excretory urogram which will show diminished or absent function when performed early and which may show extravasation of the excreted medium when performed later than several days following the injury, retrograde pyelography will delineate the degree of renal injury whether performed immediately or several days later In bladder injury proper diagnosis is made by the retrograde opaque cystogram In urethral injury, correct diagnosis is made by failure of a urethral catheter to pass or by the extravasation of medium on an opaque urethrogram or cystogram Bleeding from the urethra independent of urination should suggest injury of the urethra distal to the external sphincter Inability to urinate may be due to injury of either the urethra or bladder

Treatment of the injury, as established, should be by the choice of the attending urologist according to his personal opinions as formed from reports in the literature and his personal experience No dictum is made for the acceptance of the classifications and recommendations of any particular investigator

Careful followup examinations should be made of all injured kidneys for the possible development of atrophy, hypertension, calculus formation, perirenal abscess and perirenal cyst Pelouze[15] was probably the first to call attention to this when he stated that ' where a palliative course has been pursued with seeming success, it is well to make a study of the comparative functional values of the two kidneys a year or so after recovery, for later complete cessation of function of the injured kidney is not altogether rare "

It is suggested that an attempt be made on a regional level to inform the general practitioner and general surgeon in the diagnosis and treatment of urinary tract injuries, particularly in localities where no qualified urological consultation and treatment are available It is further suggested that the care of such injuries should always be in the hands of the urologist in such places as he may be available

SUMMARY

The present concepts of the diagnosis and management of urinary tract injuries have been briefly reviewed Several case histories illustrating certain pitfalls in the diagnosis and treatment of such injuries have been presented Suggestions for the diagnosis and treatment of urinary tract injuries are submitted

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MULTIPLE UNRELATED PRIMARY MALIGNANCIES OF THE GENITOURINARY TRACT

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Billroth, in 1869, was the first to report multiple primary malignancies occurring in the same patient[1] Since then reports of similar cases have appeared with increasing frequency[2-16] Multiple papillary neoplasms of the urinary tract were well presented in these reports[17-22] Multiple *unrelated* primary tumors within the same tract or system of an individual are rare and very few references to such a finding were encountered in a review of the literature[22-24]

During the last year, several patients with unrelated multiple malignancies of the genitourinary tract were seen in the Squier Urological Clinic Because of the interest which these cases aroused, we reviewed our pathological files and found a total of 27 cases with variegated neoplastic lesions among approximately 5000 urological cancer specimens

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We included in the series, those cases *only* that met the following criteria

1) The tumors had to arise from different tissues of the same or different organs of the genitourinary tract The histological picture of malignancy had to differ in each and the tumor had to be independent of one another

2) The neoplasm could be coexistent or one might precede the other, but otherwise they always had to have the above requirements

We excluded from the series, not only our cases with multiple carcinomas of the urothelium, but also the so-called benign hypertrophy of the prostate that was associated with benign or malignant lesions of other portions of the genitourinary tract Finally we omitted metastatic lesions

CLINICOPATHOLOGICAL FINDINGS

1) In the 27 cases there were 26 males and 1 female and the age range was from 16 to 76 years

2) In 23 cases both types of malignancies were coexistent and in 4 cases the malignancies followed one another

3) In 13 cases with coexistent malignancies we found
   a) 1 case in which both tumors were asymptomatic,
   b) 9 cases in which both tumors produced symptoms,
   c) 13 cases in which one tumor gave symptoms and the other was silent

4) In 3 of 4 cases in which malignancies were not coexistent, symptoms were present

5) The presence of one malignancy was suspected clinically in all the cases, and in 15 cases the presence of two malignancies was also clinically known In the remaining 12 cases the second malignancy was an incidental pathological finding

6) There was a total of 54 tumors of which 48 were located in different organs and 6 were found in the same organ each with a different histological pattern

7) The 48 tumors were located as follows

In the urothelium	20
a) renal pelvis	3
b) bladder	14
c) urethra	3
In the prostate	13
In the kidney	9
In the penis	4
In the adrenal gland	1
In the seminal vesicles	1

8) The 6 tumors that developed in the same organ were located as follows

In the bladder	4
In the kidney	2

9) The following combinations were found

A tumor in the prostate and a tumor in the urothelium	10 times
A tumor in the kidney (*parenchyma*) and a tumor in the urothelium	7 times
A tumor in the penis and a tumor in the urothelium	3 times
A tumor in the adrenal and a tumor in the kidney	1 time
A tumor in the kidney and a tumor in the prostate	1 time
A tumor in the prostate and a tumor in the seminal vesicles	1 time
A tumor in the penis and a tumor in the prostate	1 time

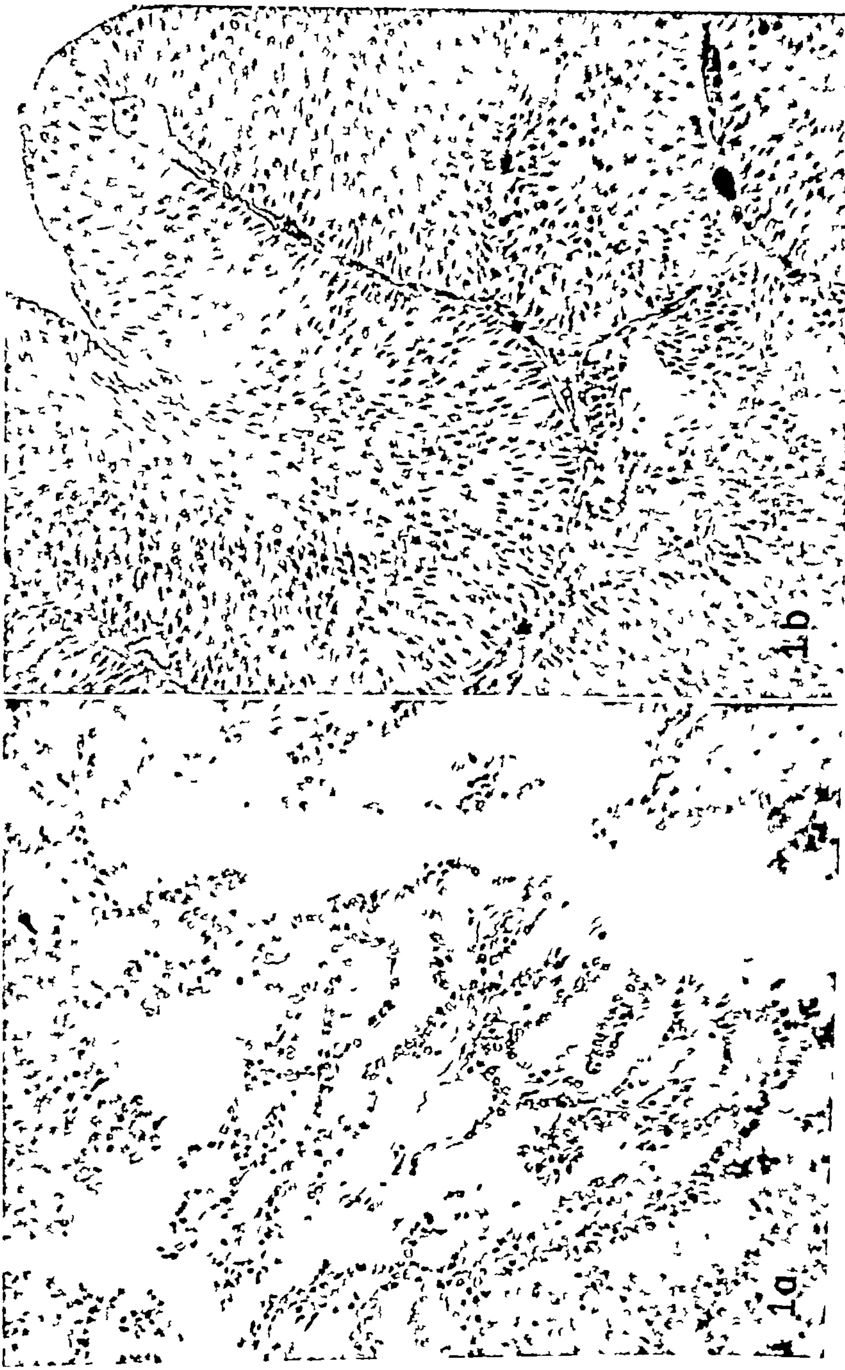

Fig 1 *a*, Papillary cysto adenocarcinoma of kidney *b*, Papillary carcinoma of bladder

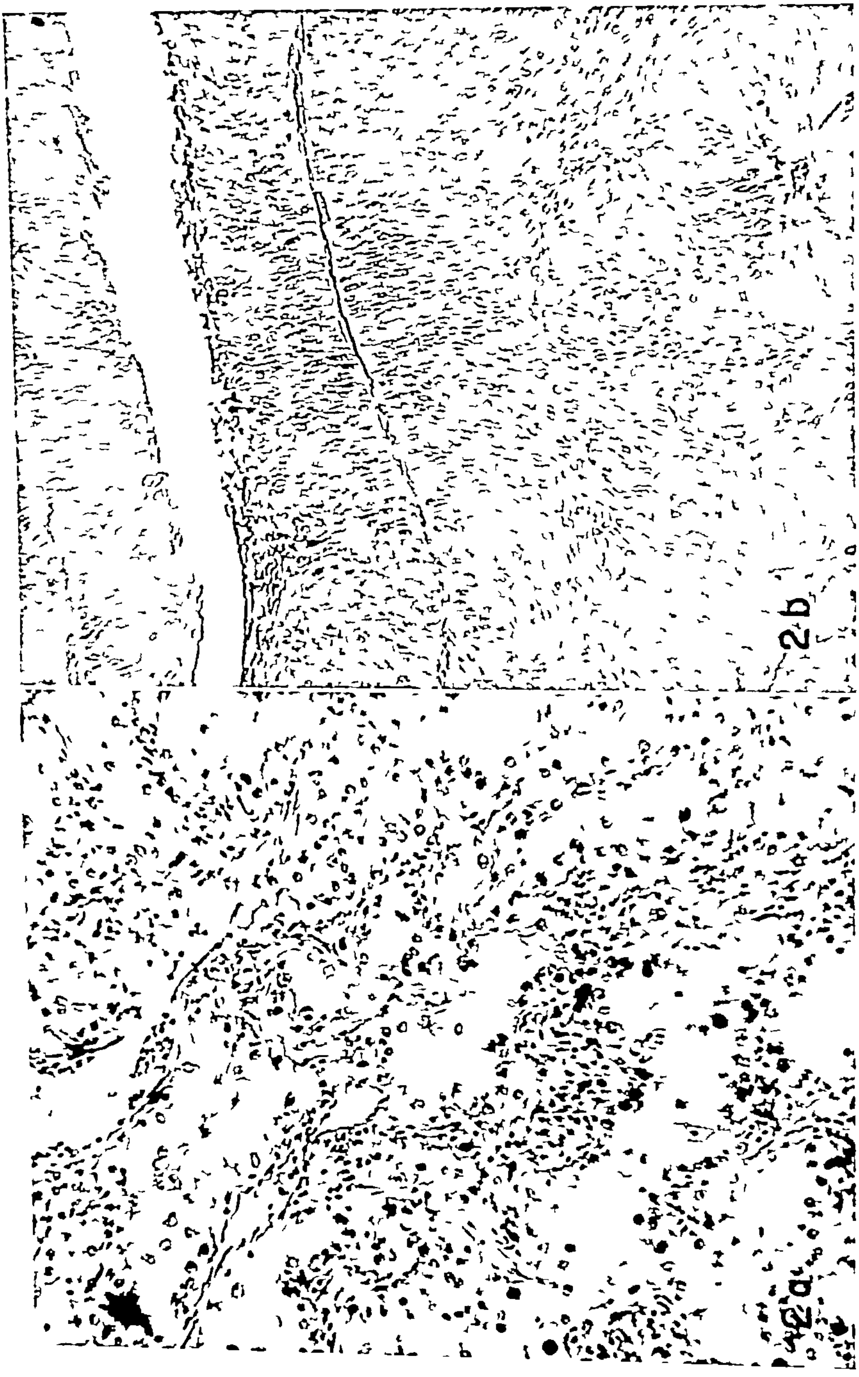

FIG 2 *a*, Clear cell carcinoma of kidney *b*, Papillary carcinoma of bladder

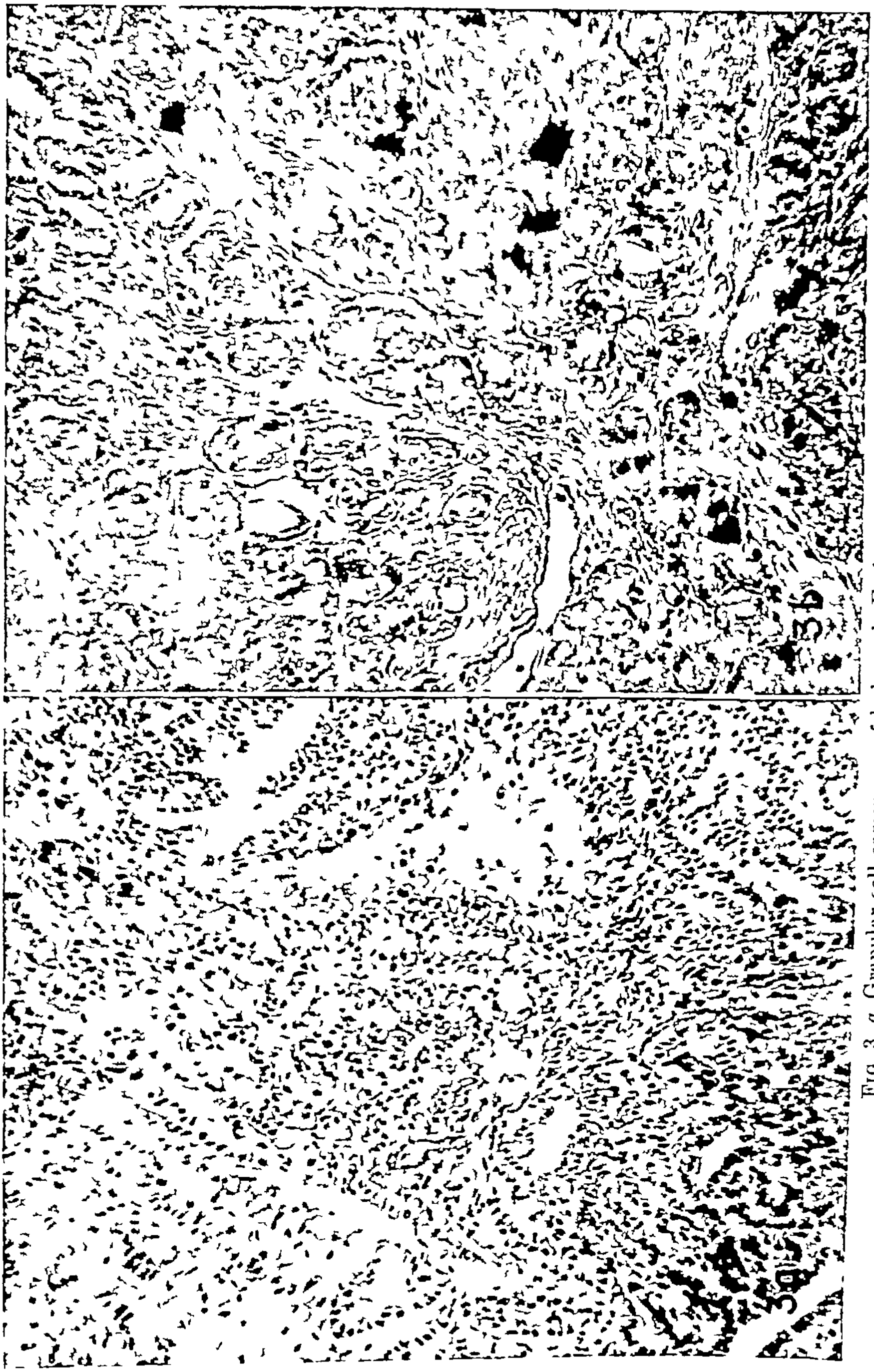

Fig 3 a, Granular cell carcinoma of kidney b, Early carcinoma of prostate

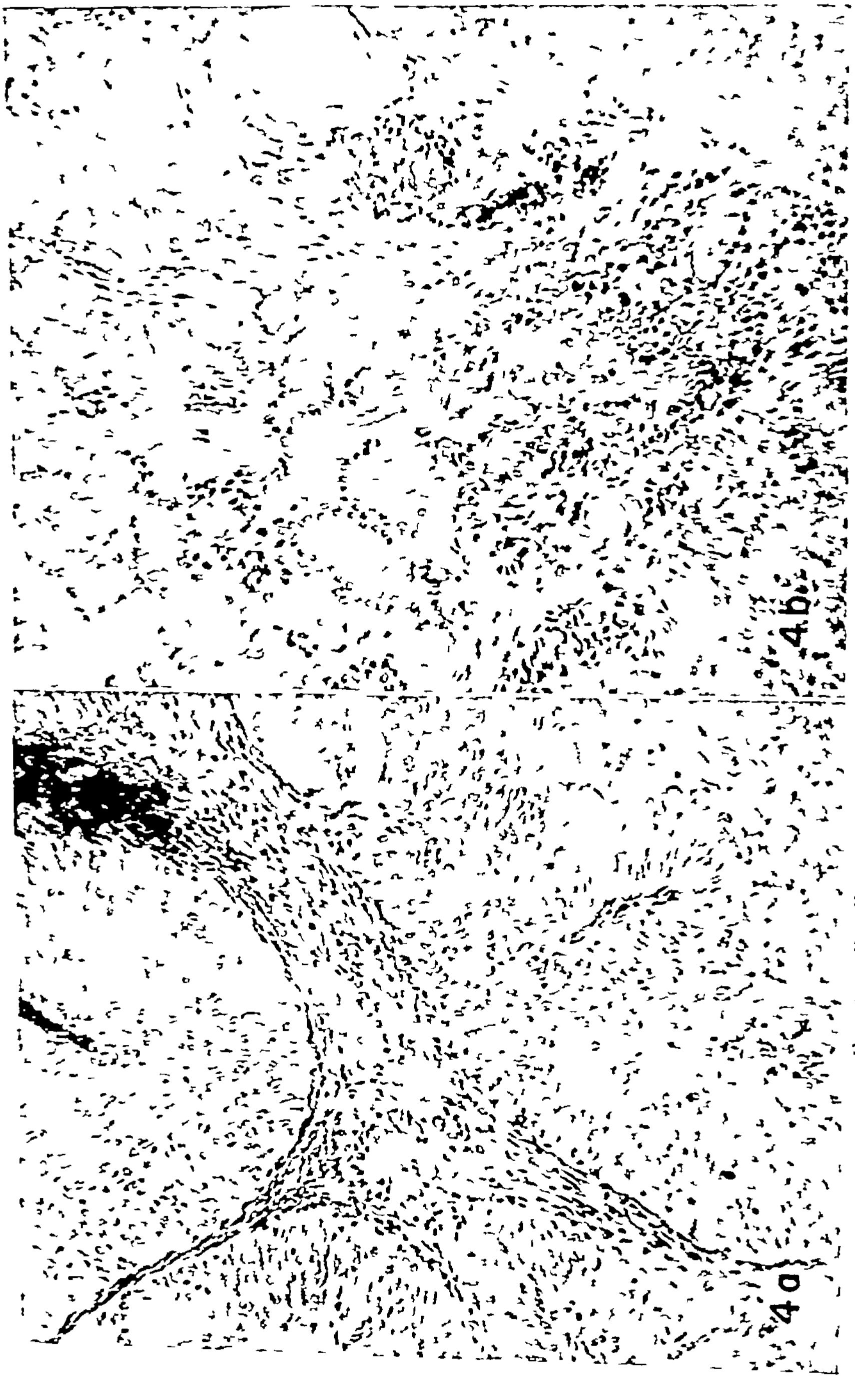

FIG 4 a, Papillary carcinoma of bladder b, Carcinoma of prostate

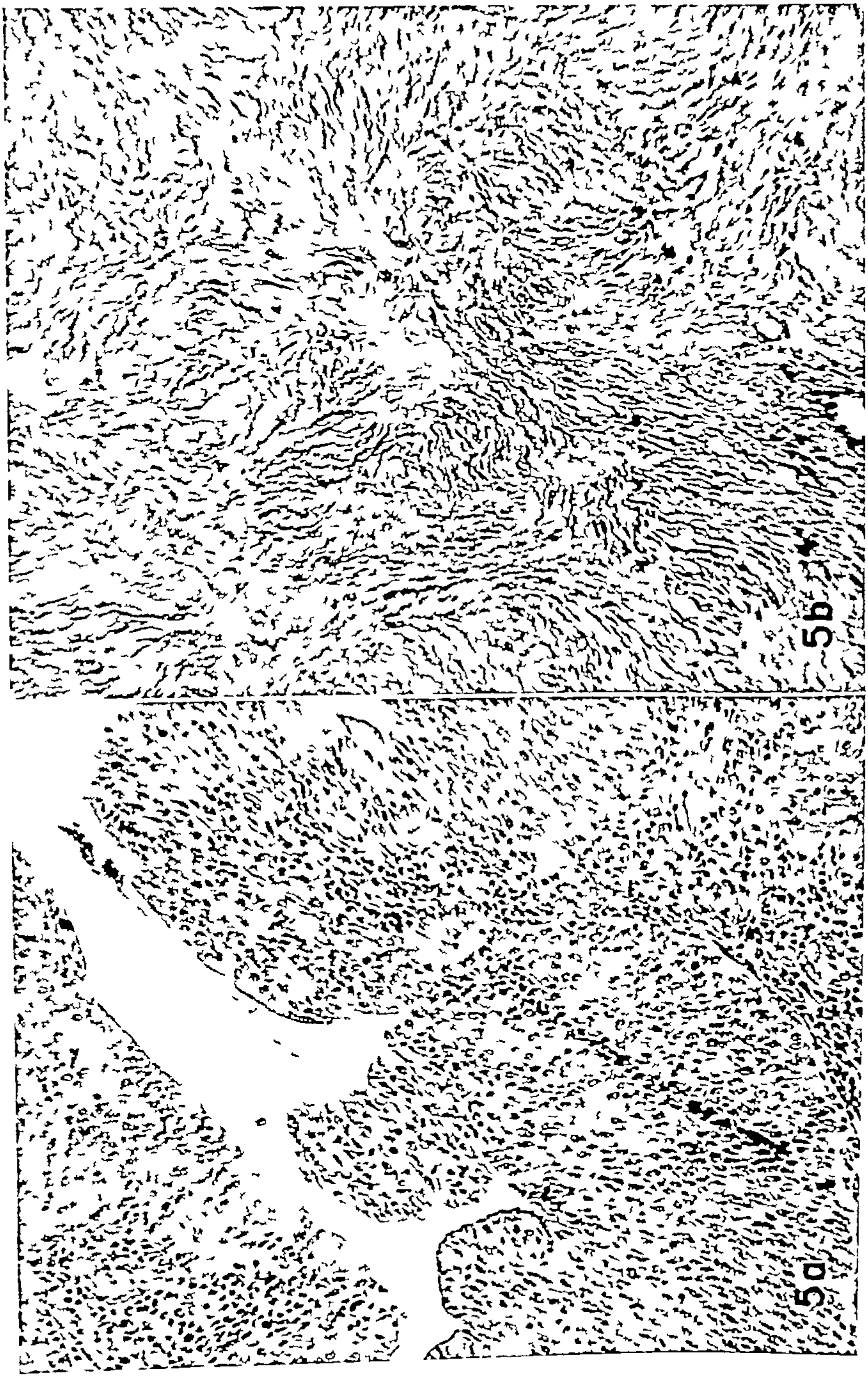

FIG 5 *a*, Papillary carcinoma of bladder *b*, Myosarcoma of bladder

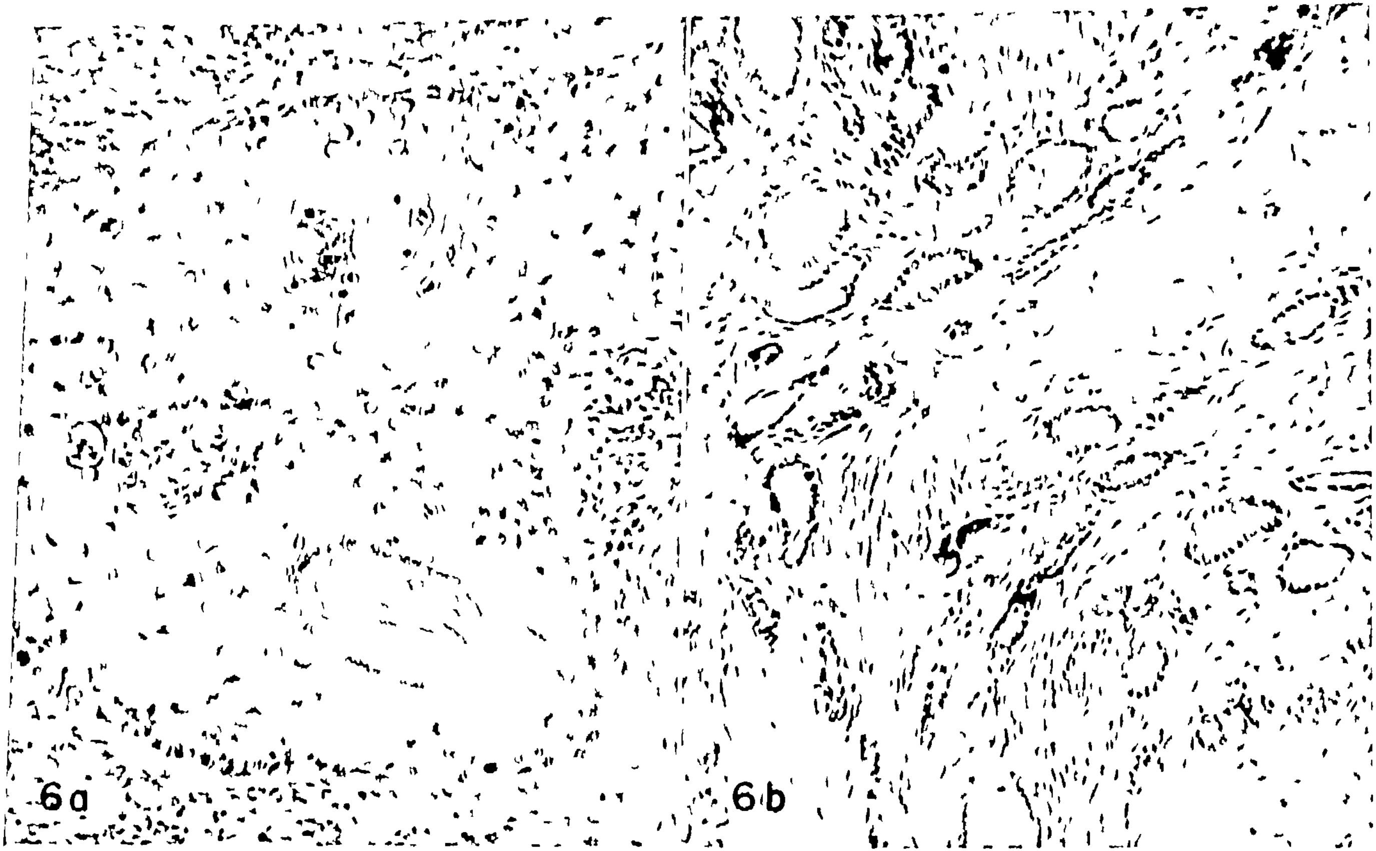

FIG 6 *a*, Squamous cell carcinoma of shaft of penis *b*, Carcinoma of prostate

10) The following were the pathological diagnoses in the above cases
   - a) Adrenal adenoma plus clear cell carcinoma of the kidney
   - b) Hemangioma of renal pelvis plus myxoma of kidney
   - c) Papillary cyst carcinoma of kidney plus papillary carcinoma of renal pelvis
   - d) Clear cell carcinoma of kidney plus papilloma of major calyx
   - e) Clear cell carcinoma of kidney plus papilloma of ureteropelvic junction
   - f) Cystadenoma of kidney plus papillary carcinoma of urinary bladder
   - g) Papillary cystadenocarcinoma of kidney plus papillary carcinoma of bladder (fig 1)
   - h) Clear cell carcinoma of kidney plus papillary carcinoma of bladder (fig 2)
   - i) Granular cell carcinoma of kidney plus early carcinoma of prostate (fig 3)
   - j) Papillary carcinoma of bladder, grade 1, plus early carcinoma of prostate
   - k) Papillary carcinoma of bladder, grade 1, plus early carcinoma of prostate
   - l) Papillary carcinoma of bladder, grades 3 and 4, plus early carcinoma of prostate
   - m) Papillary carcinoma of bladder plus carcinoma of prostate
   - n) Papillary carcinoma of bladder plus carcinoma of prostate (fig 4)
   - o) Carcinoma of urinary bladder, grade 3, plus early carcinoma of prostate
   - p) Papillary carcinoma of bladder, grade 1, plus myxosarcoma of bladder (fig 5)
   - r) Papillary carcinoma of bladder, grades 2 and 3, plus hemangioma of urinary bladder
   - s) Carcinoma of the prostate plus papillary carcinoma of posterior urethra
   - t) Carcinoma of prostate plus carcinoma of seminal vesicles
   - u) Bowenoid disease of the glans penis, plus papilloma of urinary bladder
   - v) Squamous cell carcinoma of penis, plus papillary carcinoma of urethra
   - w) Squamous cell carcinoma of shaft of penis, plus carcinoma of prostate (fig 6)
   - y) Intraepithelial carcinoma of the glans penis, plus papillary carcinoma of urethra

CONCLUSIONS

We have presented 27 cases of multiple primary malignancies of the genitourinary tract that were found among 4000 urological neoplasms from the Squier Urological Clinic

All were proven to have two different malignancies In 12 cases the additional malignancy was an incidental pathological finding, and in the rest the two conditions were suspected clinically

In our series only those cases that met the following criteria were included

1) The tumors had to arise from different tissues in the same or different organ of the genitourinary tract Therefore, the histological pictures of malignancy were different in each and the tumors were independent of one another

2) They could be coexistent or subsequent, but otherwise they always had met the above requirements

We excluded from the series our cases with multiple carcinomas of the urothelium, benign hypertrophy of the prostate gland that was associated with benign or malignant lesions of the genito-urinary tract and finally metastatic lesions

3) We wish to emphasize that multiple primary malignancies in the same patient can occur and that they are not so rare as is the general impression among urologists It is important that we keep in mind the possibility of their occurrence for only then can early diagnosis be made and adequate treatment instituted

We wish to thank Dr John K Lattimer, director of the Squier Urological Clinic, for suggestions

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ANALYSIS OF TIDAL DRAINAGE MALFUNCTION

SHERWOOD A JACOBSON

The introduction of tidal drainage into the care of the paralyzed bladder by Munro and Hahn[1] was of the greatest value This one device performed three functions 1) drained the bladder, 2) irrigated the bladder, 3) exercised the bladder in the same way that a physiotherapist would exercise a weak or paralyzed extremity However, the original devices were complicated, and the modes of dysfunction were ill understood A considerable simplification has been made but even the simplest devices (figures 1 and 2) need constant and devoted care The proneness of all types of tidal drainage to malfunctions has led many physicians to abandon its use and for some even to doubt the soundness of its theory [2]

This study represents a notation of the manifestations of malfunction with an analysis of the reasons for the malfunction This has resulted in development of an apparatus that can be trusted to work properly with a bare minimum of care All of the observations were checked by the appropriate apparatus attached to a model bladder (large rubber balloon) and by bedside observation

Figures 1 and 2 show the two simplest devices described and as designated they will be called type A[3] and type B[4] in this paper Type A has the air vent for breaking of the siphon as a small hole in the drip bulb as shown or similarly by means of a hypodermic needle put into the tubing above or below the drip bulb A frequent difficulty with this arrangement is irrigating solution dripping from the needle or air vent Examination of the apparatus at this time shows that the solution has collected in the section of the system immediately adjacent to the air vent This collection usually completely occludes the tubing or bulb at this point with a considerable amount of air trapped in the tubing below the drip bulb This situation leads to malfunction of the apparatus plus the irritation of the ward personnel because of a continuous puddle under the apparatus which often leaves a stain on the floor This often will produce a state of non-co-operation on the part of the ward personnel which may lead to the banishment of the apparatus from the ward

The fluid in the needle or air vent is not dislodged by the negative pressure of the siphonage This is because of the high degree of capillary tension produced by the fluid in the small lumen of the needle or air vent In such a situation the siphonage will stop because of the large degree of negative pressure in the system rather than because of the entrance of air The bladder may be partially filled or empty at this time This state of affairs once established persists because as fluid enters the system from above, it is immediately siphoned into the drainage

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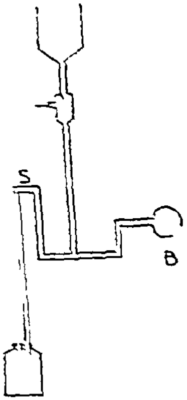

Fig 1

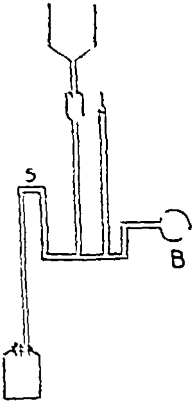

Fig 2

Fig 1 Tidal drainage apparatus described by Lawrie and Nathan[3] It is called type A for purposes of discussion in this paper

Fig 2 Tidal drainage apparatus described by Bellis[4] It is called type B for purposes of discussion in this paper

bottle without changing the situation. The needle once plugged with fluid rarely clears spontaneously. In fact the longer the fluid blockage remains the more permanent it becomes because of the precipitation of salts and corrosion. It is quite a serious matter if the bladder has not emptied when the system becomes static in this manner for this mixture of fluid and urine in the bladder acts as a residual urine. This soon becomes infected if it is not already and the infection flares even with chemotherapy. If the bladder is empty when this situation presents it is less serious but the tidal action on the bladder is lost. An identical situation can occur in the type B system when fluid is pushed into the needle at the end of the side arm by air being entrapped in the tubing below the drip bulb.

At times the fluid will drip out of the needle as quickly as it comes down from the overhead bottle. Then the bladder receives no fluid except for the urine coming from the kidneys which will eventually cause the siphon to act. Once the siphon starts it leads to the static situation described in the previous paragraph.

In both the types A and B system a considerable amount of air is caught in the tubing below the drip bulb with fluid backing up into the drip bulb. When this happens one or a combination of several things may occur. The first is one of the ward or floor staff sees the filled bulb and turns the system off. The second is that the system may work properly despite periodic filling of the drip bulb. This spontaneous return of function is very rare in the type A system because of the ease of blockage of the nearby air vent. The usual occurrence is a premature breaking of the siphon by the air in the tubing after normal siphon action has started especially in the type B system. This last situation may be present without complete filling of the drip bulb. This premature breaking of the siphon can occur frequently enough to rarely or never empty the bladder with the inevitable infection.

To avoid the vulnerability of the entrance point of air and the tendency of the simple drip bulb to entrap air in the system the following modification was made (fig 3) A needle was attached to the lower end of the drip bulb by a short section of tubing and the lower end of the tubing attached to the hub of the needle so that the solution flows through the needle The shaft of the needle should be placed in the open upper end of a meter length of glass tubing taped vertically to an intravenous stand and the tip of the needle against the inner wall of the tubing The lumen of the piece of glass should be at least 0 5 cm in diameter and the larger tube the better to prevent capillary attraction from impeding the action of the apparatus The open end of the glass tubing allows air to enter during siphonage and this size tubing is too large to form a water block A bit of sterile gauze may be fastened lightly over the opening to prevent the entrance of micro-organisms but so tight as to prevent a free flow of air An additional advantage to the use of the hypodermic needle in this manner is that the rate of flow of the solution into the bladder can be determined by the size of needle used When this type of control is used, an adjustable clamp does not have to be placed on the tubing below the reservoir and the rate of flow cannot be accidentally changed The glass tubing allows the apparatus to be used as a cytometer when the siphon segment is clamped and a ruler is placed alongside the glass

The level of the lowest portion (Y of fig 4) of the tubing from the drip bulb which meets the tube from the bladder is of great importance The distance the bladder is above 'Y' equals the amount of negative pressure exerted on the bladder at the end of siphonage That is because at the end of siphonage a negative pressure is exerted on the bladder as determined by the column of water equal in height of the bladder above Y This is shown diagrammatically by figure 4 A certain amount of negative pressure is needed to completely empty the flaccid bladder with stiffening of the walls secondary to infection which is quite common If the bladder is not emptied the infection will flare even with chemotherapy For general use the five centimeters below the symphysis pubis recommended by Munro[5] works very well This setting should be checked in each case by measuring the residual in the bladder immediately after the completion of siphonage The presence of a residual indicates that 'Y' should be lowered further If 'Y' is set too low, bleeding from the bladder may occur because of too great negative pressure causing rupture of small vessels in the bladder wall

The presence of air in the bladder can often cause difficulty because during the emptying of the bladder this air can get into the siphon and cause breaking of the siphon before the bladder is empty This makes the bladder liable to infection because of the residual urine and prevents the full effect of the tidal movement which tends to produce a rigid bladder wall The most important way air can get into the bladder is where there is no dependent tubing between the bladder and the Y (see figs 1 and 2) For when this is so, on completion of siphon action there is air at Y and a negative pressure acting in the bladder with the result that air will be sucked into the bladder There should be a dependent U between the bladder and Y to act as a trap which should be about five centimeters to each arm If it is too long enough fluid can be caught in it to act as a residual urine and as area for the origin of infection However a trap of tubing which is five centimeters long on each limb would contain less than five cubic centimeters which would not be a problem Another means of air entering the bladder is when the patient is detached from the apparatus This is less important than the above situation for the patient is detached from the apparatus less often It still can reduce the effectiveness of the apparatus and so when initially attaching the apparatus to the patient the air from both the tubing and the bladder should be carefully expelled Then the Foley catheter and the inflow tube should be clamped separately when separating them for manipulation or turning of the patient

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[5] Munro, D The Treatment of Injuries to the Nervous System Philadelphia W B Saunders Co , 1952

Because of the inertia of the bladder wall on siphonage, the rest of the system will empty before the bladder This difficulty has been avoided in tidal apparatus in the past by the slowing of the inflow of air with the use of a small hypodermic needle or other quite small orifice As has been pointed out above, this very small lumen inflow point is very fertile soil for difficulty Slowing the outflow of the

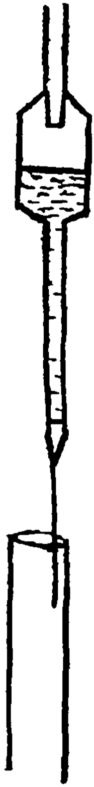

FIG 3

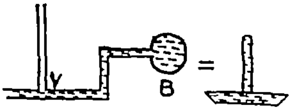

FIG 4

FIG 3 Details of air intake and fluid flow from drip bulb

FIG 4 Diagram of Y and bladder segment of tidal drainage at end of siphon action, with
ction of distance of bladder above Y as column of water tending to produce negative force
bladder

fluid by incorporating small lumen tubing in the siphon (fig 5) has been found to work very well The 3 mm diameter of lumen plastic tubing from the usual commercial disposable intravenous set does admirably Also with the use of this small tubing there seems to be less tendency for premature breakage of the siphon action when air has gotten into the system

Another source of malfunction is when there is no air vent on the waste bottle or when the air vent there is blocked This will usually result in the siphon action stopping with the siphon tubing full and there is the risk of overdistension of the bladder A similar situation exists with a kinked siphon tube

The end of the siphon tube which discharges into the waste bottle should be so situated that it is well above the surface of the waste liquid If the tip is below the surface and the bottle is lifted there can be back siphonage of contaminated fluid into the system and lead to a urinary infection

Blockage in the catheter is sometimes a cause of failure of tidal drainage to function properly The apparatus will show rapid filling and emptying with a clear, colorless or pale fluid in the waste bottle This is with a steadily increasing area of dullness above the symphysis pubis

The matter of placement of the siphon is beyond the scope of this paper Munro[5] and others have covered it quite well in their writings

The apparatus (fig 5) described above is quite simple to assemble Usually used for the reservoir of irrigation fluid is a Murphy drip bottle with the attached drip bulb tubing and clamp although the usual inverted intravenous bottle works as well but is less convenient The bottle is hung from an intravenous stand with about a foot of attached tubing and then the drip bulb followed by a few inches of rubber tubing terminating in a number twenty intravenous needle The shaft of this is put inside the lumen of a large bore glass tube (over 0 5 cm in diameter) about two to three feet in length Caution should be exercised that the hub of the needle does not block or narrow the upper opening of the tubing It is important that the tip of the needle touch the inside of the tubing without obstruction of outflow from the needle The glass tubing and the hub of the needle are taped to

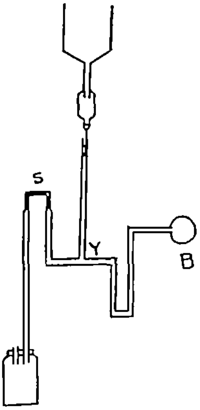

FIG 5 Diagram of tidal drainage apparatus described in this article

the pole of the intravenous stand The lower end of the glass tubing is attached to a short length of rubber tubing which, in turn, is attached to a glass Y-tube This is taped to the pole as well and the limbs of the Y have each a length of medium bore rubber tubing attached to them One of these goes to the catheter and is attached to it by means of a glass adapter The other tubing forms the siphon segment and the siphon itself is a piece of narrow tubing One of the sterile polyethylene tubes on the market for the administration of intravenous fluids does very well This is taped to the pole too The end of the siphon segment is put in a waste bottle The whole apparatus should be sterile and can be made up in a single pack that will easily fit into a hospital autoclave

SUMMARY

A discussion of the cause of difficulties of function of tidal drainage apparatuses has been presented and a trouble free apparatus has been described

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FATAL AIR EMBOLISM DURING PRESACRAL INSUFFLATION OF AIR

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In 1950 Ruiz Rivas[1] described presacral insufflation of air as a diagnostic procedure to visualize the intra-abdominal organs Since then this method has been fairly widely employed in clinical medicine as a diagnostic aid in patients suspected of having intra-abdominal tumors, especially pheochromocytoma Several authors have reported on the use of this procedure and have emphasized its simplicity, efficacy and safety

Air embolism with fatal outcome as a sequel to presacral air insufflation has rarely been described Wilhelm[2] reported that one of his patients, an elderly female, developed air embolism after 800 cc of air was injected and died 15 minutes later At autopsy a large amount of air was found in the right heart chambers and in the larger and smaller veins Another of his patients had chills, high fever and jaundice within 36 hours after presacral air insufflation a "large retroperitoneal" phlegm developed on the right side, "wide surgical drainage and antibiotics" were of no avail and the patient died Another instance of serious air embolism was reported by Russ et al [3], the patient, a 74-year-old woman, after injection of 600 cc of oxygen, suddenly became cyanotic, the skin was clammy, blood pressure was unobtainable and a loud mill-wheel type of murmur was heard with each heart beat The patient responded to treatment and gradually recovered

In general, however, presacral insufflation has not been followed by any significant morbidity or mortality, this is in contrast to the experience with perirenal insufflation which "has been abandoned in many institutions because of the frequency with which air embolism occurs during the procedure "[4]

The following brief case report is another instance of fatal air embolism following presacral air insufflation

A 47-year-old Negro was admitted to the hospital on September 21, 1955 He stated that in 1939 or 1940 he was told that he had high blood pressure While under observation in the hospital, his blood pressure was found to be paroxysmal in character and fluctuated between 216/140 and 150/100 In addition, he was found to have diabetes mellitus and arteriolar nephrosclerosis An intravenous regitine test was positive for pheochromocytoma, the intravenous benodiane and intramuscular regitine tests, however were negative On November 9, 1955, presacral air insufflation was done and 1300 cc of air injected Immediately after

Accepted for publication July 10, 1956

[1] Ruiz Rivas, M Generalized subserous emphysema through a single puncture Am J Roentgenol , **64** 723–734, 1950

[2] Wilhelm, S F Gas insufflation through the lumbar and presacral routes Surg , Gynec & Obst , **99** 319–323, 1954

[3] Russ, F N , Glenn, D I and Gianturco, C Gas embolism during extraperitoneal insufflation Recovery in the left decubitus position Radiology, **61** 637–638, 1953

[4] Steinbach, H L , Lyon R P , Smith D R and Miller, E R Extraperitoneal pneumography Radiology **59** 167–176, 1952

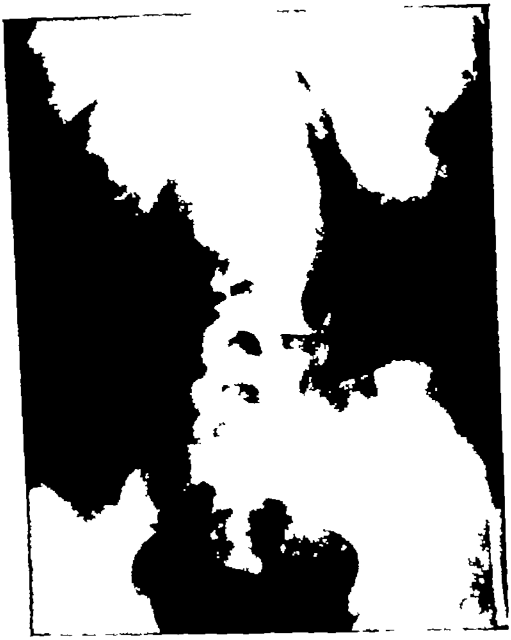

FIG 1

moving the patient from the knee-chest to the prone position acute hyperpnea developed, he lost consciousness stopped breathing and his pulse was unobtainable He was immediately placed in the left lateral decubitus position and artificial respiration, intubation oxygen, and intracardiac epinephrin were administered He did not respond to these measures and died Roentgen examination of the abdomen after death revealed considerable amount of air in the retroperitoneal space and outlined the kidneys adequately (fig 1) At postmortem examination air was found retroperitoneally in the region of both kidneys Slight bulging of the right antrum was noted and air bubbles were present in the coronary vessels The right ventricle was opened under water and air was seen to escape from it Marked coronary artery sclerosis was found one large vessel was almost completely occluded by atheromatous material and the small vessels showed marked intimal thickening The adrenal glands were normal in size shape and consistency The renal arteries and arterioles showed concentric thickening and in the glomeruli varying degrees of hyalinization were found

COMMENT

This unfortunate experience led to a review of the literature dealing with presacral air insufflation Several reports were found and reviewed The pertinent data are recorded in table 1 These authors emphasized the following advantages of presacral air insufflation The method provides information which is unobtainable by another method requires no premedication, may be carried out in 15 minutes patient walks out of the examining room to resume his normal activities, only one puncture is needed to visualize both kidneys and other abdominal organs the retrorectal space is easily penetrated by the needle and is easily accessible it is avascular and therefore embolism improbable the only

TABLE 1

	No Cases	Complications
Blackwood[5]	15	Surgical emphysema of scrotum 2, shoulder tip pain with sense of constriction in epigastrium 1
Duff et al [6]	Not stated	Puncture of rectum 2, scrotal emphysema 1, emphysema of abdominal wall 3, cervical emphysema 2, mild substernal pressure with dyspnea 2, fullness in loins and epigastrium is common
J Gershon Cohen et al [7]	Not stated	Patient experiences practically no discomfort and walks out of examining room to resume his normal activities
Lerman et al [8]	Over 200	None stated
Reese and MacLean[9]	20	Surgical emphysema up to neck 1, "About half complained of pain in tip of shoulder Almost all patients complain of a feeling of distention but this soon passes off "
Renfer[10]	28	None stated
Russ et al [3]	Not stated	Air embolism 1, see text
Senger et al [11]	Over 100	Not stated
Steinbach et al [4]	60	"1 patient complained of more than mild discomfort "
Wilhelm[2]	67	Air embolism 1, see text Infection 1 See text
Mosca* collected	1500	"Without fatal accidents "

* Quoted by Russ[3]

contraindication is an inflammatory process in region of anus and presacral space, it is easy to perform, is reliable and extraordinarily safe

At this hospital presacral air insufflation was performed in approximately 14 patients[12] prior to the case which is the subject of this report The procedure is carried out by the members of the genitourinary staff of the hospital by the following technique

The patient is placed in the knee-chest position After appropriate sterilization of the skin a small novocain wheal is made in the skin just ventral to the tip of the coccyx An 18 gauge needle is inserted through the wheal and its point is guided by the gloved left index finger in the rectum so that the point of the needle is just anterior to the sacrum A short piece of flexible rubber tubing is attached to the hub of the needle to the distal end of which a 50 cc syringe with a two-way stopcock is adapted The plunger of the syringe is then withdrawn to make certain that the needle is not in a blood vessel If no blood is obtained, 5 cc of sterile saline solution are injected, followed by aspiration as an additional precautionary measure The air is then injected slowly in 50 cc amounts until 1000–1500 cc are introduced During the entire procedure, care is taken to keep the needle stationary and aspiration is done frequently to make certain that the needle is not in a blood vessel Following the injection of air, the patient is placed on the x-ray table and a series of films are taken

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[5] Blackwood, J Presacral perirenal pneumography Brit J Surg , **39** 111-119 1951-52

[6] Duff, J , Kenyon, H R and Hyman, R M Pyelography in combination with simultaneous retroperitoneal pneumography J Urol **70** 963-968 1953

[7] Gershon Cohen, J , Levins, S and Hermel, M B Retroperitoneal pneumography by injection of oxygen into the presacral space Am J Roentgenol , Rad Ther & Nuclear Med **68** 391-394, 1952

[8] Lerman, F , Harper, J G M , Hertzberg, A D , Berman M H and Lerman P H Presacral air injection J Urol , **70** 312-317, 1953

[9] Reese, L and MacLean, J T Presacral insufflation of oxygen for outlining the contents of the retroperitoneal space Canad M A J , **67** 632-637, 1952

[10] Renfer, H R Pneumoretroperitoneum by presacral insufflation Radiol Clin **22** 29-43, 1953 (In German) Abstract in Radiology, **61** 857 1953

[11] Senger, F L Horton, G R , Bottone, J J , Chin H Y H and Wilson, M C Perirenal air insufflation by the paracoccygeal retrorectal route New York State J Med , **53** 2823-2826, 1953

[12] Bradley, Wm S Personal communications

The following sequellae have been noted at this hospital following the procedure Pain over the epigastrium accompanied by "choking" sensation gas on stomach ', dull aching retrosternal pain, abdominal discomfort pain over the left upper quadrant of abdomen, pain in the shoulders on deep inspiration, subcutaneous emphysema of abdomen, external genitals, neck free air under the diaphragm and mediastinal emphysema All of these were of brief duration and disappeared spontaneously in a few hours to several days

The cause of the air embolism was not definitely determined The air was injected slowly in 50 cc amounts During the procedure aspiration was carried out repeatedly to insure that the needle was not in a blood vessel The presence of the large amount of free air in the retroperitoneal space indicates that only a fraction of the total air injected gained entrance into the vascular system It is conjectural whether the air was injected into a vein directly or whether the air entered a vessel as it dissected its way through the retroperitoneal tissues At any rate it is very disconcerting that occasionally a fatal outcome results following what is commonly believed to be, an innocuous and a useful diagnostic procedure In an attempt to prevent serious and fatal complications, Wilhelm[2] suggested that the following precautionary measures be taken during the performance of presacral air insufflation 1) strict aseptic conditions, 2) the use of a blunt canula-like needle with a sharp obdurator, 3) slow injection of gas 4) Insufflation should be done with the patient in the left lateral position whenever possible, 5) constant observation of patient during entire procedure 6) A resuscitator and stimulants should be at hand In addition to these, the following precautionary measures are suggested Auscultation of the heart during the entire procedure to detect the mill-wheel[13] type of murmur in case it occurs readiness to manually massage the heart and stimulate it electrically in event of cardiac arrest

SUMMARY

An instance of fatal air embolism following presacral air insufflation is reported

The related literature is briefly reviewed

Certain preventive measures are suggested to eliminate air embolization

The writer expresses his appreciation to Dr Wm S Bradley, chief of the Genito-Urinary Section Veterans Administration Medical Teaching Group Hospital for supplying the description of the technique of presacral air insufflation, and to the Medical Illustration Laboratory for preparing the photograph

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[13] Durant T M Long J and Oppenheimer, M J Pulmonary (venous) air embolism Am Heart J 33 269–281, 1947

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MALE FERTILITY REVIEW OF 200 SEMEN ANALYSES AND THE USE OF PREGNENOLONE THERAPY

H K TURLEY AND J L SHAW

As urologists we are asked to examine and to treat the infertile male When the voluminous articles on seminal inadequacy are reviewed, there are controversies on the technique of semen analysis, there is inability to agree on normal and subnormal studies, and, worst of all, the many forms of therapy, the results of which are most discouraging Much credit is due to the larger sterility clinics and the brilliant work of such persons as MacLeod, Hotchkiss, Bunge, Tyler, Abarbonel, Charny, Farris, and the many others who have helped clarify and standardize this intriguing subject Urologists in smaller communities where sterility clinics are not available must accept this problem and perform studies and treatment that will most likely benefit the patient Our paper, directed to this latter group, discusses semen analyses and followup reports with particular reference to the use of pregnenolone as a therapeutic agent in stimulating spermatogenesis

One can find the technique of semen analysis adequately described in the textbooks, FERTILITY IN MEN, by Hotchkiss[1] or HUMAN FERTILITY, by Farris[2] It should be emphasized that all specimens must be collected by masturbation or coitus interruptus following three to four days of sexual abstinence Patients should be excluded if they have had an acute illness during the past month In making the count, both chambers should be counted and their results averaged If there is considerable discrepancy, the count should be repeated There should be at least two semen analyses done before treatment is considered In examining for motility, the disc method of Hotchkiss is perhaps the simplest and yet fairly accurate This is done by placing a disc in the ocular with a one-quarter area cut out Both the active and inactive cells are counted Each number is multiplied by four to determine the number present in the entire microscopic field Motility is a difficult end point to assess under the best of conditions It must depend upon the judgment, skill, and experience of the observer The specimen should stand at room temperature for 2 hours after being collected before being examined for the first time It should be examined again at 8 hours as a critical end point of motility duration

The American Society for the Study of Sterility[3] proposed minimal "normal" standards as follows The seminal ejaculate should liquify in ten to thirty minutes with an average volume of two to four cubic centimeters and with a minimum count of 40 million spermatozoa per cubic centimeter or a minimal total of 125–150 million There should not be more than 20 per cent abnormal heads on

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Read at annual meeting, Southeastern Section of American Urological Association Hollywood Beach, Fla March 25–29, 1956

[1] Hotchkiss, R Fertility in Men Philadelphia J P Lippincott Co 1944

[2] Farris E Human Fertility and Problems of the Male Palisades Park Author's Press 1950

[3] White A Symposium on Steroids in Experimental and Clinical Practice New York The Blakiston Co , 1951

TABLE 1 *Results of 100 semen analyses from infertile marriages Treatment with vitamins and/or thyroid only*

Normal Fertility	
No children	27 (27%)
Subsequent children	22 (22%)
Subnormal Fertility	
No children	41 (41%)
Subsequent children	10 (10%)

the stained smear Motility should be present in at least 25 per cent of the eight hours post-ejaculation, at room temperature Some investigators as MacLeod and Gold[4] believe the minimal normal should be even lower A count of 20 million per cubic centimeter with 40 per cent active in 2 hours, or approximately 20 million active spermatozoa in the ejaculate would constitute the lower limits of "normal" They find a strong relationship between motile activity and fertility, and very little relationship between sperm count and fertility above the level of 20 million per cubic centimeter

Infertility may be defined as the inability of a couple to conceive after a year of normal marital endeavor During the years 1948 through 1953, two hundred consecutive semen analyses were studied on men from infertile marriages The criteria as proposed by the American Society for the Study of Fertility were used Normal fertility was found in 82 men or 41 per cent Subnormal fertility was found in 118 or 59 per cent, and azoospermia was present in 32 or 16 per cent Testicular biopsy was done on 5 patients, or approximately 16 per cent of the azoospermia group The remainder refused this procedure Only one patient revealed suitable studies for vasoepididymal anastomosis This operation appeared to be unsuccessful on the first examination soon after surgery, and since then, contact has been lost

One hundred cases of infertility and their outcomes were reviewed after a minimum of 2 years These men received no treatment except the administration of multiple vitamins A few patients, however, did receive thyroid when the basal metabolic rate was found below (minus 15) See table 1 Cases showing azoospermia were excluded

TREATMENT

Pregnenolone,[5] a steroid, the 3-hydroxy analogue of progesterone, was used in the treatment of seminal inadequacy Its actions are distinctive and are not readily traced to the formation of other steroids It has adrenocorticoactivity as desoxycorticosterone, but of lower intensity Evidence suggests an absence of toxic actions in man In a few there were some constitutional effects, such as an increased libido However, in most cases, there was a feeling of well-being and greater stamina The exact mechanism by which pregnenolone may exert a helpful influence upon seminal inadequacy in the human remains to be determined

[4] MacLeod J and Gold, R Male factor in fertility and infertility, sperm morphology in fertile and infertile marriage J Fertil & Steril 2 394, 1951

[5] Henderson, E Weinberg M and Wright W Pregnenolone endocrine review J Clin Endocrinol 10 455 1950

TABLE 2 *Report of 40 cases using pregnenolone therapy*

Pregnancy	
Completed	6 (15%)/20%
Interrupted	2 (5%)/
50% improvement sperm population and/or motility	15 (37 5%)
Improved motility 50% or over	13 (32 5)
Improved sperm population 50% or over	8 (20%)
No improvement or less than 50%	25 (62 5%)

Three (3) cases in which pregnancy ensued could not be followed by sperm counts and these were not included in the improvement percentages

The suggestion has been offered by Gassner,[3] "That the fertilizing capacity of the sperm is perhaps enhanced by some changes in the enzyme systems, or that fructose secretion is stimulated "

Pregnenolone was administered intramuscularly in aqueous suspension, giving 50 mg once a week for 4 injections, then 100 mg once a week for 4 weeks, and finally, 150 mg once a week for three or four injections The sperm population showed a decided decrease in many counts done within 3 months of treatment Therefore, most studies were performed 6 months after treatment was begun From 1951 through 1953, only 40 cases that received pregnenolone could be reported (table 2) These were considered to have had adequate followup studies Men with azoospermia and normal counts were not treated There was an over-all improvement, that is, at least a 50 per cent increase in sperm population and/or motility in 37 5 per cent of the 40 cases Eight wives of the 40 patients, or 20 per cent, became pregnant within a year of treatment although two aborted A second pregnancy occurred in 1 case 2 years later, following a second course of pregnenolone A second pregnancy occurred in another case without additional treatment These results are presented to stimulate interest in this preparation, realizing no clinical significance can be attached to such a limited study

Gonadotrophins were used in a few of the earlier cases, but the response was not impressive

Testosterone was given to a number of these patients, but followup studies were not satisfactory and the results certainly are not conclusive The general response appeared to be less favorable than when pregnenolone was used Charny[6] reports an over-all improvement in 18 5 per cent using 2400 to 2700 mg of testosterone during a 12 to 18-week period Tyler and Singher[7] reported that the administration of lipotropic substances produced the best results statistically, but the percentage of improvement was only 14 9 per cent They state that, "medicinal therapy for the infertile male is relatively disappointing, but the patient's spermatogenic function may be utilized to possible greater advantage by pooling frozen-thawed partitioned ejaculates in certain instances " Their studies of seminal fructose and 17-ketosteroids show little correlation between endocrine hypogonadism and male infertility

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[6] Charny, C Treatment of male infertility with large doses of testosterone J A M A, 160 98 1956

[7] Tyler, E and Singher, H Male infertility, status of treatment prevention and current research J A M A, 160 91 1956

The concensus of opinion at the present time is that vitamins in the normally nourished man will not improve deficient spermatogenesis

Coital advice should be given in all cases of infertility The method advised by Farris is recommended When the man is subfertile, coitus should be concentrated twice on the approximate day of ovulation When the man is highly fertile, coitus for three successive days during the selected period should be advised

COMMENT

While seminal inadequacy may exist, the couple should be made to realize this apparent inadequacy is only a relative one, depending primarily upon the fertility potential of the wife From the economic standpoint of the patient it is probably wise to withhold the more expensive biopsies, hormonal assays, and prolonged treatments until their value can be proven The larger sterility clinics can better carry out these studies with less economic loss to the patient Testicular biopsies should be done in azoospermia to select cases suitable for surgical anastomosis It is of doubtful value in oligospermia for the purpose of prognosis and treatment at the present time Remember, the layman considers virility and fertility as the same Therefore, from the psychosomatic viewpoint, the husband must never be told it is his fault that infertility exists In the same token, even though azoospermia exists, they should not be told that pregnancy is impossible

SUMMARY

Some aspects of the technique of semen analysis and minimal normal standards are discussed The incidence of fertility in 200 semen analyses is given There are 100 cases of infertility reported, with a 2-year followup Treatment in general of seminal inadequacy is discussed

Forty cases have been reported in which pregnenolone was the therapeutic agent in the treatment of semen inadequacy These results show a pregnancy rate of 20 per cent and an over-all improvement of 37 5 per cent However, it should be re-emphasized that little clinical significance can be obtained from so few cases It is believed that pregnenolone is a relatively safe drug and the treatment is not prolonged nor is it expensive

As a urologist, the task of treatment and the study of male infertility is a difficult one, since only the male side of the problem is at our disposal However, it is necessary to accept this challenge even though the present treatments are discouraging

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A FLEXIBLE OBTURATOR FOR STERN-McCARTHY RESECTOSCOPE SHEATHS

HARRY N WEBSTER, JR

This obturator (fig 1) is an adaptation of the coudé olive tip catheter fashioned to obturate the sheath of the Stern-McCarthy resectoscope and its variations The obturator consists of a metal handle and interchangeable plastic coudé tips The handle is marked proximally to orient the curve of the tip and, distally, is arranged with a screw thread to fasten the tip and a metal projection which fits in the lumen of the coudé tip to maintain proper alignment of the tip to the beak of the sheath

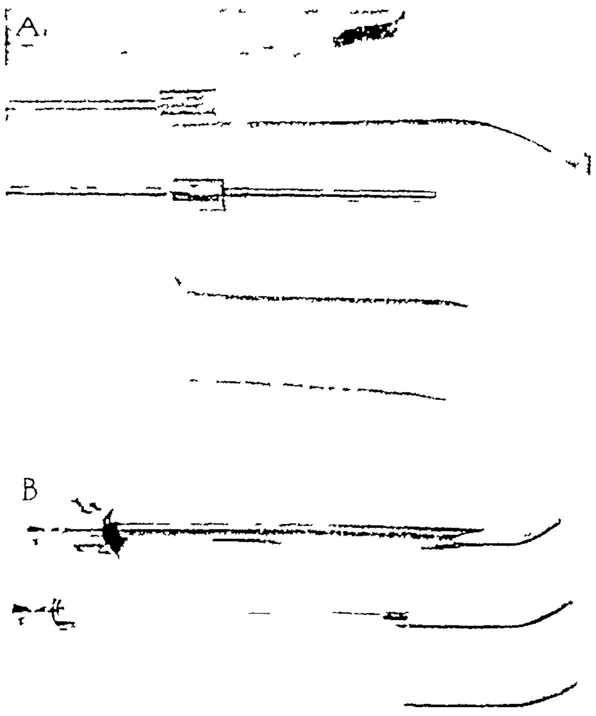

Fig 1 *A*, detail of obturator tip *B*, obturator in relation to sheath

The coudé tips are made of flexible plastic material moulded with a central canal to accept the threaded tip of the handle The tips are interchangeable to fit the various sheath sizes

To use the obturator, it is assembled with a tip to match the sheath size, then lubricated with jelly and inserted through the sheath until the handle seats

Read at annual meeting Southeastern Section of American Urological Association Hollywood Beach, Fla March 25-29 1956 firmly in the cone of the sheath and the curve of the coudé tip is properly aligned The maneuver of introduction is the same as that used with conventional obturators

I have used the obturator for the past 6 months with satisfactory results It allows the tip of the sheath to ride over the hyperplastic median lobe almost as easily as does a coudé catheter

The obturator design may be adapted to obturate any straight sheath and it is planned to alter the panendoscope sheath for this purpose

The obturator is made by the National Electric Instrument Co

610 Van Antwerp Bldg , Mobile, Ala

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MODIFICATION OF THE STERN-McCARTHY RESECTOSCOPE SHEATH

EDWIN W BROWN

Re-examination postoperatively of a number of my cases of transurethral resection of the prostate disclosed a small to moderate amount of tissue remaining at the apex, usually extending from the midline anteriorly to the three o'clock area and counter clockwise to the eight or nine o'clock area The Ritter resectoscope-loop was awkward in my hands and its use, I discontinued I endeavored to revise the Stern-McCarthy resectoscope sheath in order to use the conventional electrotome and loop, yet at the same time to eliminate the beak of the sheath that prevents the apical tissue from dropping down into view This was easily accomplished by filing the bakelite sheath down to the dimensions shown in figure 1

I have used the revised sheath in approximately 100 resections and have experienced no difficulty with its use, that is, capsular perforations, lens fogging or arcing out of bulbs On the other hand, tissue removal has been far more complete

613 Guaranty Bldg , West Palm Beach, Fla

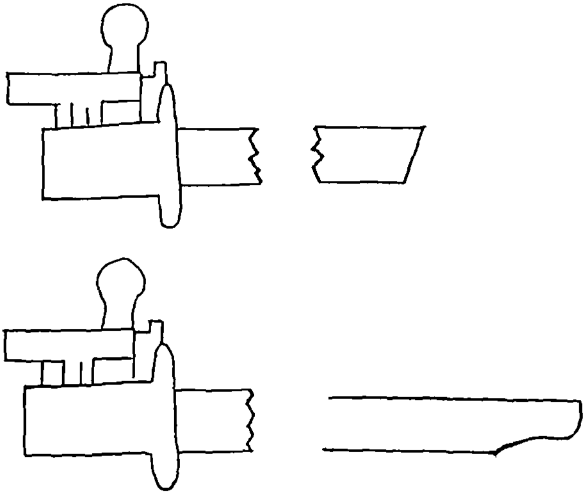

FIG 1

Read at annual meeting, Southeastern Section of American Urological Association, Hollywood Beach, Fla , March 25-29, 1956

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THE TREATMENT OF HYDRONEPHROSIS BY SACRAL RHIZOTOMY IN PARAPLEGICS

JOHN A HUTCH*

From the California Rehabilitation Center, Vallejo, Calif

In a previous paper[1] this author attempted to answer the question "why may a person who sustains a transection of his spinal cord develop hydroureter and hydronephrosis and die in uremia?" He contended that intense, erratic nervous impulses originating in the distal stump of the spinal cord caused the bladder to become small, contracted and trabeculated He felt that the general process of bladder trabeculation caused a saccule or diverticulum to occur in that part of the bladder wall through which the ureter passed It was his contention that such a saccule so damaged the intravesical ureter that reflux and a functional obstruction in the lower ureter resulted These two factors, working together or alone, resulted in dilatation of the upper urinary tract The conclusion was reached that the dilatation of the upper urinary tract in such cases could be stopped if this process could be halted at its inception This would involve interrupting those nerve roots which carried the impulses from the distal stump of the spinal cord to the bladder

This paper presents 4 cases in which this thesis has been applied clinically Each patient was a paraplegic with a transection of the spinal cord well above the sacral segment Each patient had a small, contracted, trabeculated bladder with dilatation of the upper urinary tract In each instance the intravesical segment of the dilated ureter was involved in saccule formation Dramatic improvement resulted in all 4 cases following bladder denervation Bladder capacity increased from 200 per cent to 600 per cent Bladder trabeculation reduced correspondingly Saccule formation disappeared and the upper urinary tracts lost their dilatation and returned to normal as judged by excretory urograms

CASE REPORTS

Case 1 H G , a 44-year-old white man, suffered an incomplete paraplegia at D12 on June 7, 1949, the result of a fall from a telephone pole His urologic history revealed that for the first 18 months after his injury he had chills and fever once or twice a month Since that time they have been less severe but chills and fever have complicated the clinical course since his injury He frequently had bilateral pain suggestive of renal origin

His upper urinary tract had been carefully followed by excretory urography from the first year of his injury In July 1952, it was noted that marked hydronephrosis and caliectasis of the left kidney and a marked dilatation and tortuosity of his left ureter were developing (fig 1, *A*) Repeated cystograms had failed to reveal any reflux (fig 1, *B*) They did show a very small and heavily trabeculated bladder Cystometric studies (fig 2) in July 1952 revealed a bladder capacity

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Read at annual meeting of Western Section of American Urological Association San Francisco Calif April 30-May 3, 1956

* Present address 2100 Monument Blvd , Pleasant Hill, Calif

[1] Hutch J A J Urol 71 412 1954

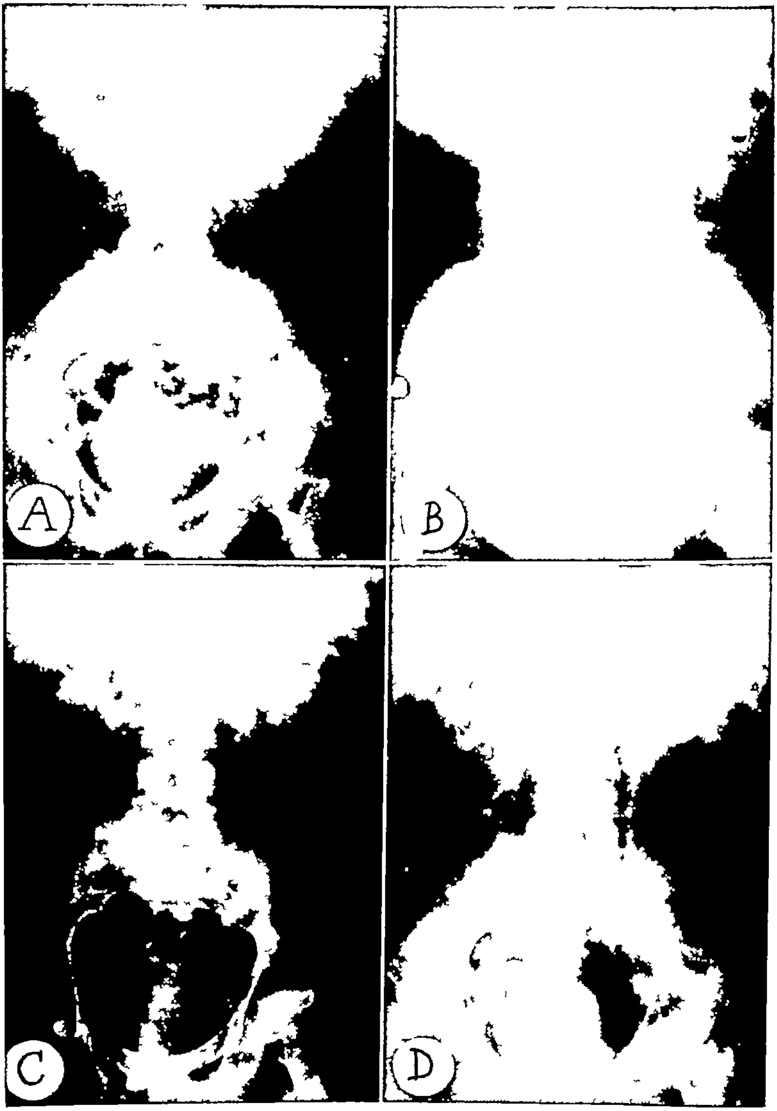

FIG 1 Case 1 A, excretory urogram prior to rhizotomy B, cystogram before rhizotomy C, 3-month postoperative excretory urogram, slight improvement D, 6 month postoperative excretory urogram, definite improvement

varying from 50 cc to 100 cc of water with rapid rise in passive pressure and many spastic contractions After the bladder had filled to between 50 cc and 100 cc it would contract and force the water out over the top of the cystometric tube Cystoscopic examination revealed a small, heavily trabeculated bladder with marked saccule formation at the site of each ureteral orifice

On July 30, 1952, the patient was given a spinal anesthetic and his bladder capacity increased to 175 cc water It was felt that if we could make permanent the interruption of the sacral nerve roots running to the bladder that we could

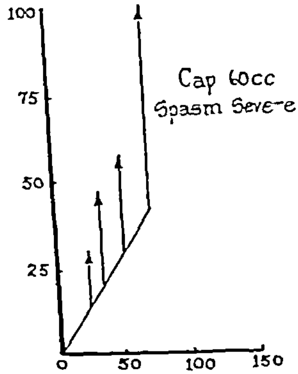

FIG 2

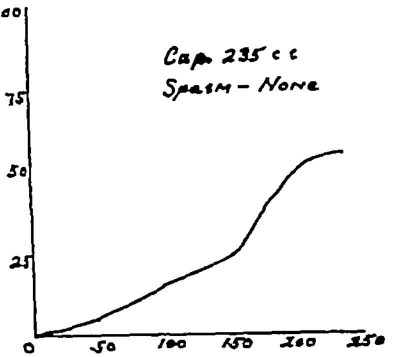

FIG 3

FIG 2 Case 1 Cystometrogram showed small bladder capacity, severe spasm
FIG 3 Case 1 Cystometrogram made 15 months after rhizotomy

free his bladder from the impulses which were causing the bladder to be trabeculated and thus favorably influence the upper urinary tract

This case was more difficult than a complete lesion because the patient had some function in his legs and it was decided that an effort should be made to block these nerves by instilling alcohol into the second, third and fourth sacral nerve roots This was done in September 1952 with little change in his urologic status In January 1953, a sacral rhizotomy, including the anterior and posterior roots of the second, third and fourth sacral nerves, was performed This was done without the loss of any remaining motor or sensory function

The patient has been carefully followed since the time of his sacral rhizotomy There has been a gradual and progressive increase in bladder capacity so that 6 months after his sacral rhizotomy his bladder held 150 cc without spastic contraction A year and 5 months after his operation his bladder capacity had increased to 235 cc (fig 3) Associated with this has been an increase in size of the bladder on cystography and a progressive reduction in the degree of trabeculation Cystoscopically, the bladder has remained trabeculated but this remaining trabeculation has been progressively less The ureteral orifices still show saccule formation around them, but throughout a 21-month postoperative period there has been progressive tendency toward normal Repeated cystograms pre- and postoperatively have never demonstrated reflux Excretory urograms 3 months (fig 1, *C*) 6 months (fig 1, *D*) and 15 months (fig 4, *A* and *B*) postoperatively show excellent function bilaterally, normal kidneys and normal ureters pyelographically His most recent studies 21 months postoperatively (fig 4, *C*) indicate that this improvement is being maintained Clinically the patient has been greatly improved, there has been a marked reduction in chills and fever and bilateral flank pain

Case 2 B J , a 32-year-old white man, sustained a complete transection of his spinal cord at D4-D5 as a result of an automobile accident on June 10, 1953 His clinical course was marked by recurrent episodes of chills and fever Because of this a urologic examination was requested Excretory urography on December 8, 1953 revealed no demonstrable function from either kidney in 5 minutes In 15

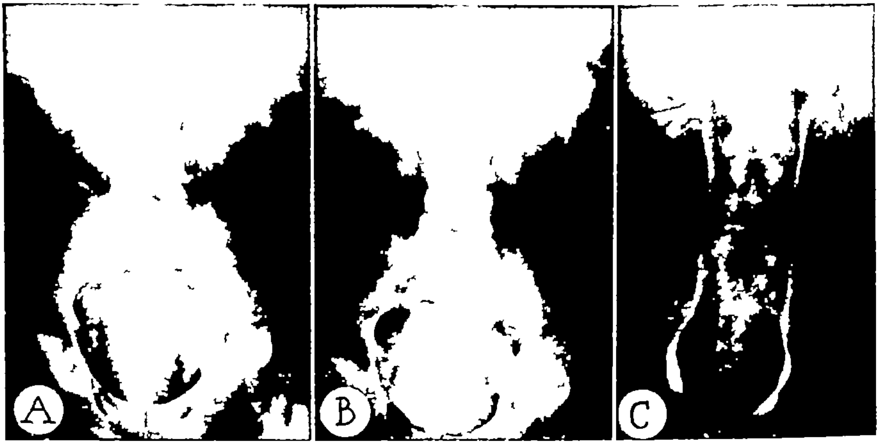

FIG 4 Case 1 *A*, excretory urogram 15 months postoperatively is almost normal *B*, cystogram 15 months after rhizotomy Note increase in bladder size *C*, retrograde pyelogram 21 months postoperatively is normal except for slight dilatation in lower ureters

minutes the left kidney showed marked hydronephrosis, its dilated calyces outlined as round puddles of contrast medium The right kidney and ureter appeared essentially normal in the 15-minute film

Cystoscopic examination revealed an almost unrecognizable bladder The bladder neck was greatly dilated The bladder capacity was so small and its walls so spastic that irrigating fluid would not fill the bladder, but rather ran back around the cystoscope Any effort to introduce water into the bladder forced the vesical walls into irregular contractions which could be observed cystoscopically The ureteral orifices were found only after prolonged search They were edematous, swollen, and lay on either end of a swollen intraureteral ridge Marked bullous edema, heavy trabeculations and deep saccules were present throughout the entire bladder above the trigone

A ureteral catheter was passed up the left ureter Residual urine (35 cc) was aspirated from this kidney Retrograde studies revealed a marked dilatation of the left ureter, pelvis and calyces

We were very concerned about this patient because of the rapid deterioration of his urinary tract (6 months since injury) We felt that these changes were due to impulses reaching the bladder from the distal stump of the spinal cord Therefore, we planned to study this patient after spinal anesthesia had temporarily destroyed these impulses to see if the urologic changes were reversible

On December 14, 1953, the patient was given a low spinal anesthetic and cystometric (fig 5) and cystoscopic examinations were repeated The bladder now held 225 cc, whereas before its capacity was under 30 cc All spastic contractions disappeared This increased capacity allowed the bladder to fill and cystoscopic examination was much more satisfactory The left ureteral orifice was surrounded by a discrete saccule The intravesical ureter ran along the floor of this saccule The orifice itself was found on the lip of the saccule The right intravesical ureter was also involved in early saccule formation The bladder was heavily trabeculated and was filled with bullous edema A cystogram was now possible and no reflux

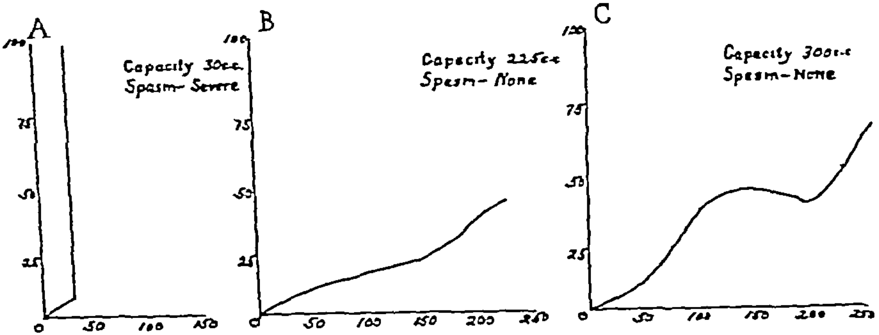

FIG 5 Case 2 *A* preoperative cystometric study *B*, preoperative cystometric study after spinal anesthesia *C*, cystometric study 1 month postoperatively

could be demonstrated We were encouraged by the changes which we observed in the bladder under the influence of spinal anesthesia The bladder capacity increased from 30 cc to 225 cc showing that these changes were reversible We felt that if we could permanently destroy these impulses which were causing bladder spasticity, we could halt or even reverse the dilatation occurring in the patient's left ureter and kidney

This was accomplished surgically on March 15, 1954 The actual operation performed consisted of exploration of the site of injury It was found that the cord was completely transected Then through a separate laminectomy incision the entire conus medullaris was removed from L1 down

A complete postoperative urologic examination was done on the fourth week The bladder capacity had increased to over 300 cc The degree of trabeculation was greatly reduced although heavy trabeculation still existed in the dome The area around the ureteral orifices was almost normal However, a slight suggestion of saccule formation could still be detected, especially on the left The bullous edema had disappeared The cystogram revealed an increase in the size of the bladder, its walls were now smooth and its contour round There was no evidence of reflux Excretory urography revealed excellent function of both kidneys in 5 minutes The calyces, pelvis and ureters were well visualized bilaterally and were normal in all respects This was a dramatic change from the preoperative pyelogram Clinically the patient was greatly improved He no longer had bouts of chills and fever, his peripheral spasm was gone and he rapidly achieved self care His bladder function was improved and he was discharged from the hospital He returned in November 1954 (8 months postoperatively) for a followup excretory urogram which was normal in all respects (fig 6)

The most recent excretory urogram was made in April 1955 (13 months after rhizotomy) It was normal in all respects

Case 3 H K a 40 year-old-white man, sustained a complete transection of his spinal cord D12 and L1 in July 1952 as a result of a coal mine cave-in accident He was admitted to this hospital in December 1952

His urologic history revealed that he was having frequent episodes of chills and fever and pain in the left flank The patient complained of severe spasms in the legs but none in the bladder to his knowledge His cystogram revealed a bladder

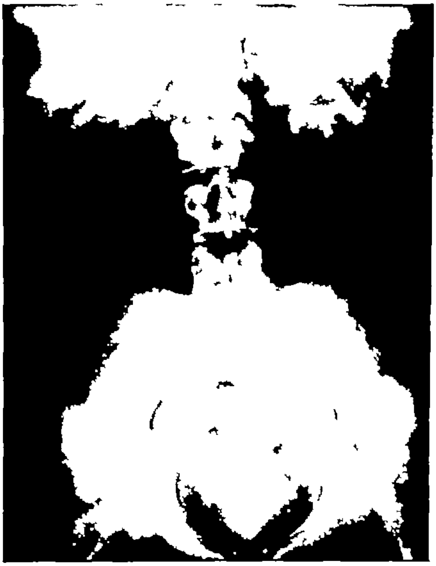

FIG 6 Case 2 Excretory urogram 8 months after rhizotomy is normal in all respects except for some residual dilatation in lower left ureter Those made 1 month and 13 months after rhizotomy are equally normal

X-rays taken before rhizotomy were lost when patient transferred to another hospital for operation Therefore, preoperative x-ray report will be reproduced for purposes of comparison " Following intravenous administration of dye, there was a delay in appearance of dye Both kidneys showed well on 15 minute film Right kidney appears relatively normal, as does right ureter Left kidney shows marked hydronephrosis, left ureter not visualized D Bell, M D , radiologist "

capacity of 300 cc with a gradual rise in passive pressure from 0 to 38 cm of water He had spastic contraction of the bladder at 125 cc fill, a spastic contraction of the bladder at 275 cc fill and he voided around the catheter at 300 cc The cystogram revealed no reflux, the bladder shadow was smooth and essentially normal in shape but slightly smaller than normal in size (fig 7, *B*) Excretory urography revealed an essentially normal right kidney with some dilatation of the lower portion of the right ureter (fig 7, *A*) There was marked dilatation of the left ureter and of the left renal pelvis Good cupping, however, was preserved in the kidney Emptying of the left kidney was poor

On initial examination we were concerned over the left kidney The patient had been a paraplegic slightly more than a year and he was beginning to show some of the changes in the upper urinary tract so characteristic of the disease The left ureter was quite dilated and the renal pelvis on the left was dilated The lower portion of the right ureter was beginning to dilate It was felt that we should follow this patient carefully and repeat his urologic examination at frequent intervals Re-examination in March 1954 showed a marked reduction in the size of the bladder and marked distortion in its shape The bladder had become much smaller than normal (fig 7, *D*) Its outline was markedly trabeculated and the bladder neck was dilated However, there was no reflux Cystometric studies at this time revealed a bladder capacity of 150 cc (fig 8) The passive pressure rose from 0 to 34 cc in 150 cc and then the bladder kicked off from spasm, emptying

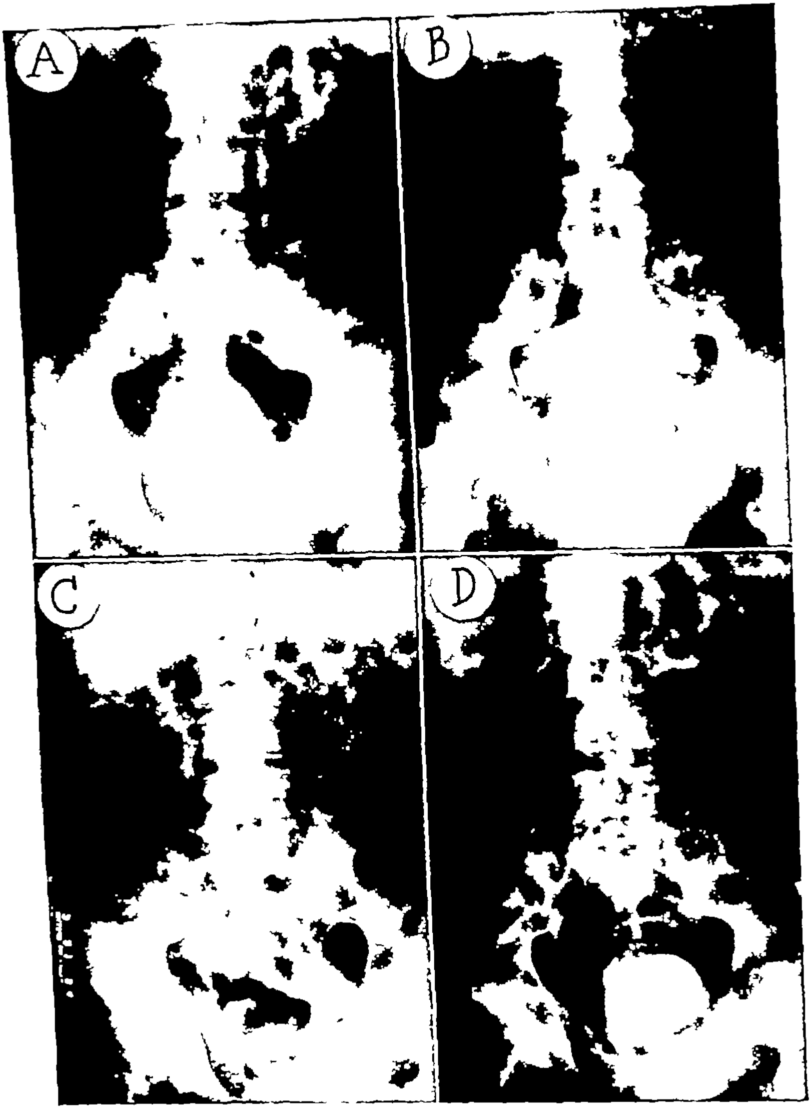

FIG 7 Case 3 A, excretory urogram 9 months after injury reveals early dilation of left ureter B cystogram 9 months after injury is still essentially normal but bladder is slightly smaller than usual C, excretory urogram and D, cystogram 21 months after injury

its contents Excretory urography revealed that the right kidney functioned well in 5 minutes and was normal throughout the pyelogram except for some progression in the dilatation in its lower third (fig 7, *C*) The left kidney did not function in 5 minutes On the 10-minute film, the dye was present in the form of five round puddles, each about the size of a quarter The 15-minute film showed marked hydronephrosis of the left kidney No dye was visualized in the left ureter throughout the course of the examination Cystoscopic examination revealed the

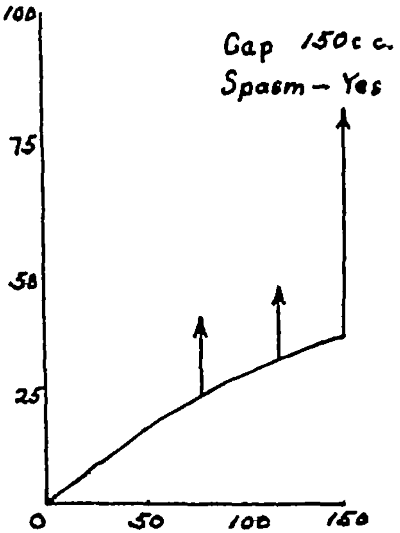

FIG 8 Case 3 Cystometric study 21 months after injury

bladder to be heavily trabeculated with distinct saccules forming around each ureteral orifice It was our feeling that this patient's upper urinary tract was undergoing serious damage and that efforts should be made to halt or, if possible, reverse this process

It was recommended by the Urology Department that the urinary bladder be denervated to free it from the impulses reaching it from the distal stump of the spinal cord It was the opinion of the staff that the distal stump of the spinal cord was doing the patient more harm than good He had a complete lesion and he had severe and disabling spasm in the part of his body supplied by the distal stump of the spinal cord It was decided to explore this patient over the conus medullaris and to remove the segment of cord below the level of his injury This was done on June 17, 1954 The patient withstood the operation well and was checked urologically 1 month postoperatively His cystoscopic examination revealed a most startling change in the bladder The capacity, which had been 150 cc, increased to 300 cc The course, heavy trabeculation present preoperatively had disappeared and only a fine mesh network of trabeculation was present The ureteral orifices which had formerly been engulfed in saccules were now converted to normal The intravesical ureter was once again firmly supported by bladder muscle behind it and was indistinguishable from normal orifices The bladder capacity, as judged by cystography, was now 300 cc (fig 9) There was no spasm The cystogram revealed no reflux and showed a bladder of normal contour, smooth outline and only slightly smaller than normal size (fig 10, *B*) A striking
chang ken place in the excretory urogram Now both kidneys showed
excel in 5 minutes, both ureters were visualized throughout their
en revealed only slight dilatation in the lower third (fig 10, *A*)
followed for 6 months postoperatively He has been
nd has maintained his progress radiologically A
of the left kidney was normal (fig 10, *C*)

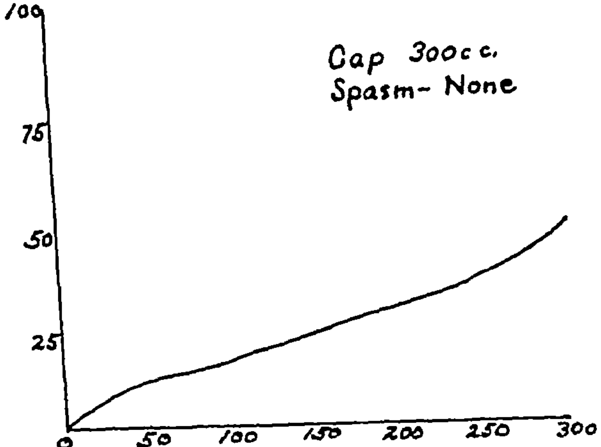

Fig 9 Case 3 Cystometric study 1 month after operation

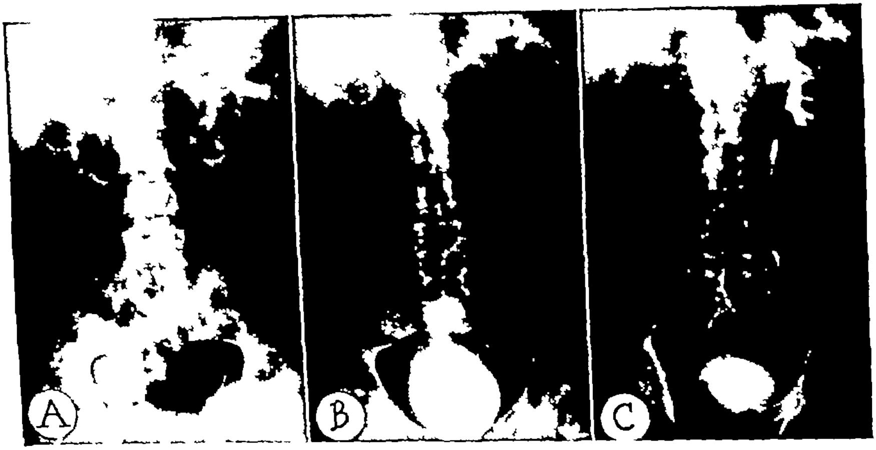

Fig 10 Case 3 *A*, excretory urogram shows good function in 5 minutes and normal contour bilaterally *B*, cystogram 1 month after operation is almost normal *C*, retrograde pyelogram 6 months after operation is essentially normal

Case 4 A fourth case will be presented briefly This case has been used before to support this hypothesis but it is so applicable, and cases of this type are so few that it will be discussed again In the Journal of Urology (August 1953) Drs H Brendler, E G Krueger, P Lerman, J S M Harper, D Bradley, M H Berman, A D Hertzberg, F Lerman and A L Dean[2] described their experiences with rhizotomy in the treatment of advanced paraplegic bladders In an effort to achieve better voiding in these patients anterior and posterior rhizotomy from T12-S5 was performed after the suggestion of Meirowsky, Scheibert and Hinchey[3] Four of these patients had severely dilated upper urinary tracts preoperatively Following rhizotomy 3 of these 4 cases showed improvement in the upper urinary tract Two were improved slightly, one was improved greatly, and

Brendler, H, Krueger, L G, Lerman, P, Harper, J G M, Bradley, D, Berman, M H, Hertzberg, A D Lerman, F and Dean, A L J Urol 70 223, 1953

[3] Meirowsky, A M, Scheibert, C D and Hinchey, J R J Neurosurg, 7 33, 1950

the fourth patient with long standing renal damage showed no change Dr A L Dean was kind enough to send me the preoperative and postoperative excretory urograms and cystograms on the patient who improved greatly

Preoperatively, this patient showed no function from either kidney by excretory urography (fig 11, *A*) The cystogram revealed a small, contracted, trabecu

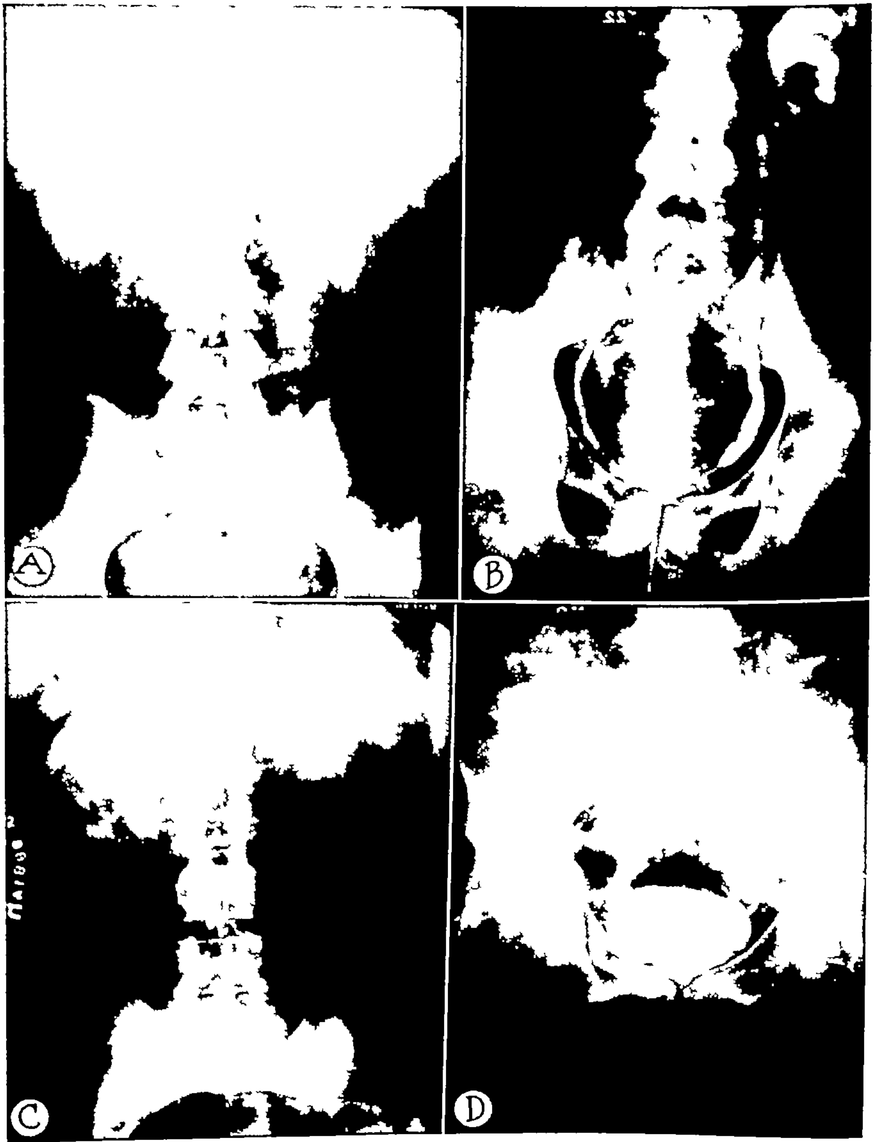

Fig 11 Case 4 *A*, preoperative 15 minute excretory urogram shows no function *B*, preoperative cystogram shows small, heavily trabeculated bladder with bilateral saccules at ureterovesical junction, bilateral reflux with dilatation and angulation of left ureter, and marked left hydronephrosis *C*, 15 minute excretory urogram after rhizotomy shows bilateral function *D*, cystogram after rhizotomy shows marked reduction in bladder trabeculation, increase in bladder capacity and disappearance of reflux except for faint trace on left

lated bladder with bilateral reflux and dilatation and angulation of the ureters (fig 11, *B*) After this bladder had been freed from its connections with the distal stump of the spinal cord by means of rhizotomy the excretory urogram showed bilateral function (fig 11, *C*) and the cystogram revealed an increased capacity of the bladder with nearly normal contour (fig 11, *D*) The reflux disappeared on the right and was reduced to a faint trace on the left

So impressed were Drs Brendler et al by the improvement they observed in the upper urinary tract following rhizotomy, that they concluded their discussion in the following manner "One wonders whether the resultant bladder relaxation, particularly in the region of the ureteral orifices, was responsible for better drainage from the upper urinary tracts in those patients whose renal function improved postoperatively Certainly this is worthy of further investigation because progressive impairment of renal function is the commonest cause of death among paraplegics "

DISCUSSION

The discussion will be limited to two considerations One is the place of bladder denervation in the treatment of the upper urinary tract in paraplegic patients The second consideration is the influence of these results upon the general theory of upper urinary tract dilatation in paraplegic patients as discussed in the introduction of this paper

Urologists entrusted with the care of paraplegic patients have employed the standard urological procedures in the treatment of cases of this kind These have included continuous bladder drainage by either the urethral or suprapubic route, tidal drainage, bladder neck resection, ureteral meatotomy and ureteroneocystotomy only to be discouraged with the results of their efforts In some of these patients the upper urinary tract dilatation progressed in spite of all of their therapeutic efforts These unfortunate patients have gone on to ultimate death from uremia or have been kept alive by some diversionary procedure above the ureterovesical junction, namely, nephrostomy or skin ureterostomy Our inability to cope with this situation undoubtedly reflects our lack of understanding of the true nature of the changes taking place

Under what circumstances should bladder denervation be employed in paraplegia? In 1951, Hutch and Bunts[4] examined 743 excretory urograms of paraplegic patients and found some degree of dilatation in 25 per cent of them In 1954 Comarr and Bors[5] studied 315 similar excretory urograms and observed dilatation in 26 per cent Comarr and Bors broke down their statistics still further and found that 12 per cent had mild dilatation, 8 per cent had moderate dilatation and 6 per cent had severe dilatation These statistics give us a perspective as to the frequency of this complication

It is in these latter two groups (those paraplegics with moderate and severe upper urinary tract dilatation) that this operation should be given a thorough clinical trial The marked improvement encountered in the 4 cases presented here is encouraging It can be hoped that this operation (or principle of treatment) will prove valuable in preventing the moderately dilated upper urinary tract from progressing to the severe stage The value of this therapeutic weapon is apparent and we must give it every chance to prove itself clinically

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[4] Hutch J A and Bunts, R C J Urol , 66 218, 1951

[5] Comarr, E and Bors, E J Urol , 74 59, 1955

What are the types of procedure which will effectively denervate the bladder? Probably the best is sacral rhizotomy in which both anterior and posterior roots are cut to all sacral segments This can be combined with a more extensive rhizotomy if occasion demands The sacral segment of the cord *per se* may be removed Subarachnoid alcohol may be injected effectively Efforts to destroy the sacral nerves in the pelvis have not proven reliable in our hands In the four cases reported here bladder denervation was accomplished by different methods In case 1, the spinous process of L5 was removed and the sacral nerves cut in the cauda equina In cases 2 and 3, the entire conus medullaris was removed This more extensive procedure was done in an effort to destroy the peripheral spasm present in these cases Case 4 had the anterior and posterior nerve roots cut from T12 through S5 While the neurosurgical procedures varied the principle of freeing the bladder from the impulses of the distal stump of the spinal cord remained unchanged in each case

What kind of a bladder is left after sacral rhizotomy? Meirowsky, Scheibert and Hinchey, Brendler et al have advocated this procedure to improve the spastic reflex bladder It is true that the autonomous bladder that develops has lost its ability to undergo sustained voiding contraction It must be remembered that the loss of the sacral nerves also destroys the internal pudendal and weakens resistance to voiding (in the same manner as an internal pudendal neurectomy) Thus, the two losses balance out and the bladder that results can be emptied by straining or with the aid of pressure on the abdomen Compared with the bladder that empties its contents every 30 to 45 minutes it is a real improvement

The apparent success of this operation has a two-fold significance First, it affords us an effective weapon with which to combat the dilatation of the upper urinary tract in paraplegic patients This has been discussed above Secondly, it lends validity to the theory upon which the operation is based The importance of this second point cannot be overemphasized as it is only through an understanding of the disease process at play that we can expect to make any real therapeutic advances

SUMMARY AND CONCLUSION

This paper deals with the treatment of hydronephrosis in paraplegic patients by means of sacral rhizotomy Reference is made to the theoretical considerations upon which such treatment is based Four cases are presented in which sacral rhizotomy was performed on paraplegic patients who had marked dilatation of the upper urinary tract In each instance careful postoperative followups showed dramatic improvement in the upper urinary tracts The discussion concerns itself with the place of such a procedure in the treatment of paraplegic patients It is also pointed out that the apparent success of this operative procedure forms quite conclusive evidence that the theory upon which the operation is based is correct

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URETEROCALYOSTOMY: A NEW SURGICAL PROCEDURE FOR CORRECTION OF URETEROPELVIC STRICTURE ASSOCIATED WITH AN INTRARENAL PELVIS

SAM G. JAMESON, J. SCHULER MCKINNEY AND JOE F. RUSHTON

Surgical treatment of hydronephrosis has brought forth many varied procedures in an attempt to improve drainage of the renal pelvis. In reviewing the literature on this subject, all of the operative procedures described are specifically designed for the extrarenal pelvis. Nowhere in the literature, to the best knowledge of the authors, is any specific operation described for the occasional, or rare, ureteropelvic stricture associated with a complete intrarenal pelvis. This problem has been unexpectedly encountered in a solitary kidney of an 8-month-old male infant, making it mandatory that a procedure be devised whereby drainage would be improved.

CASE REPORT

J. L. C., 8-month-old-white boy, was always in good health when he suffered an acute episode of gastroenteritis. Because of diarrhea and vomiting with dehydration, the patient was hospitalized and given subcutaneous fluids and antibiotics followed by improvement. He was discharged 4 days after admission. However, during the 24 hours after leaving the hospital, the mother noted that patient did not void. Generalized edema was also noted and patient was again hospitalized.

Physical examination: Temperature 100.2 degrees, pulse 140, abdomen revealed large, firm, questionably tender mass in right upper quadrant. Moderate generalized edema was present.

Laboratory determinations: Hemoglobin 10.6 gm., red blood cells 4,660,000, white blood cells 15,000, blood urea nitrogen 65.0, sodium 135 mEq/liter, potassium 5.0 mEq/liter, chlorides 90 mEq/liter, and CO2 combining power 26 volumes per cent. No urine could be obtained upon admission for urinalysis.

In spite of supportive therapy, including M/6 sodium lactate, the general condition of patient became worse during the following 24 hours and generalized edema increased. Because there was no urinary output, it was felt that cystoscopy with passage of ureteral catheters was indicated to rule out obstructive uropathy. Cystoscopy revealed congenital absence of left half of trigone and left ureteral orifice. Protruding from right ureteral orifice were several brownish colored crystals which microscopically were found to be uric acid. A 4F ureteral catheter was passed to the right renal pelvis several times. Upon removing the catheter from the ureter each time, one or more waves of urine were seen to come from the ureteral orifice. Because of the poor condition of the patient, anesthesia and instrumentation were not prolonged in order to do retrograde pyelograms at this time. It was felt that the obstruction had been relieved and

Accepted for publication September 12, 1956.

the patient was returned to his room In retrospect, it was felt that diarrhea with dehydration and acidosis had produced precipitation of uric acid crystals with subsequent blockage of ureter

Twenty-four hours following cystoscopy, it was noted that the patient still had not voided, and catheterization revealed no urine in the bladder Cystoscopy was again performed under general anesthesia, and a 4F ureteral catheter was passed to the renal pelvis and left indwelling A retrograde pyelogram at this time revealed a large filling defect in the right renal pelvis, felt to be due to uric acid crystals This catheter was left in place and the patient was returned to his room During the following 12 hours diuresis was profuse through the catheter, which was irrigated frequently with sodium bicarbonate solution in an effort to further dissolve the uric acid crystals Because the temperature by this time had risen to 105 8 degrees, the patient was started on antibiotics and chemotherapy

Three days later there was marked generalized improvement of the patient and the ureteral catheter was removed after making a retrograde pyelogram, which revealed considerable decrease in filling defect, although it was still present Following removal of catheter, the patient voided frequently with a large 24-hour volume During the following 14 days, the patient was continued on supportive therapy, chemotherapy, and antibiotics with much improvement The white blood cell count fell from 29,800 to 13,600 After receiving whole blood transfusions, the hemoglobin rose from 8 5 gm to 10 1 gm , and the red blood cells rose from 3,000,000 to 4,260,000

Twenty days after admission the patient appeared to be in good general condition, at which time an excretory urogram was made to determine whether any underlying pathological process might be present, which, in addition to the dehydration and acidosis resulting from the diarrhea, could have caused precipitation of uric acid crystals This excretory urogram confirmed the previous diagnosis of congenital absence of left kidney On the right side there was a large hydronephrotic sac, obviously secondary to a stricture of the ureteropelvic junction (fig 1, *A*) There was no evidence of uric acid crystals in the renal pelvis or calyceal system at this time

Surgical correction of this stricture was recommended to the parents, but because of the constant vigil during the preceding illness, they requested that surgery be postponed for 2 weeks in order to allow them to get away from the hospital for a few days It was felt this would not be detrimental to patient, and therefore he was discharged

The patient did well for about 8 days, but then fever and generalized edema developed Three days later he ceased voiding and was readmitted to the hospital

Physical examination Temperature 104, pulse rate 140, respiratory rate 30, abdomen revealed right kidney enlarged and tender, easily palpable below right costal margin There was marked generalized edema

Laboratory findings Hemoglobin 8 7 gm , red blood cells 2,640,000, white blood cells 26,000, blood urea nitrogen 45

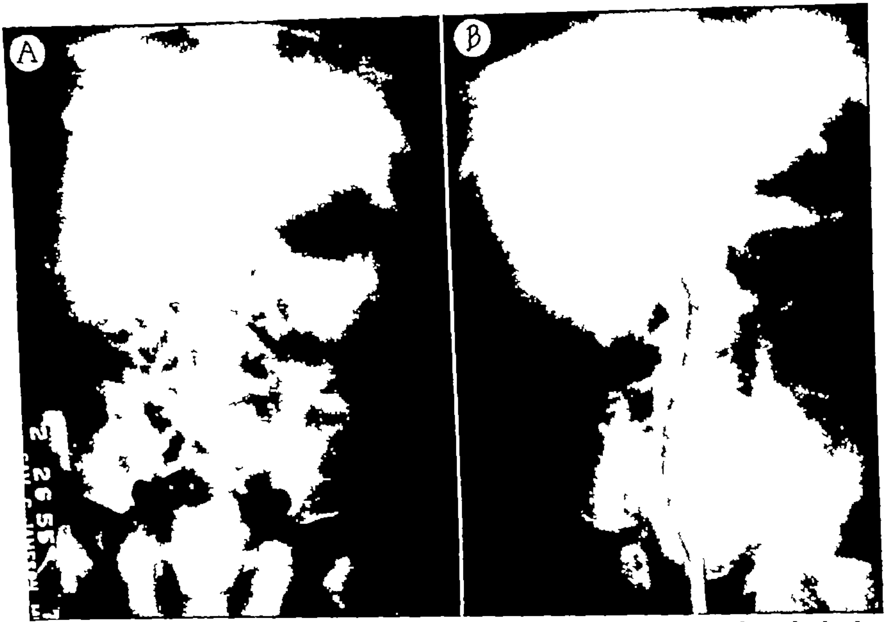

FIG 1 A, excretory urogram 20 days after admission to hospital reveals right hydronephrosis secondary to stricture of ureteropelvic junction Congenital absence of left kidney B, retrograde ureterogram 8 days following intravenous pyelogram reveals complete blockage of ureteropelvic junction secondary to inflammatory reaction and edema at site of stricture

It was felt that inflammatory reaction at site of ureteropelvic stricture resulted in enough edema to completely block drainage from the kidney

Cystoscopy was again performed under general anesthesia A 4F catheter was introduced into the right ureter, at which time a ureterogram was made (fig 1, *B*) Following this a catheter was introduced into the renal pelvis and a retrograde pyelogram made The catheter was left indwelling, there was immediate diuresis with prompt clinical improvement of patient

First operation (fig 2) Eight days after admission, the right kidney was exposed in order to repair the ureteropelvic stricture Upon dissecting hilum of kidney completely free, a marked narrowing of ureter was found immediately adjacent to the kidney for a distance of about 1 cm This stricture became more pronounced the closer the ureter approximated the kidney At this point the ureter was very pale and friable in appearance There was no evidence whatsoever that any portion of the renal pelvis extended outside the renal parenchyma To further complicate this finding, the renal artery was divided into two branches, with the slightly smaller of the two branches coursing posterior to ureter and supplying the posterior one-third of kidney Temporary occlusion of this vessel caused marked cyanosis of the posterior one-third of the kidney Therefore, it was felt that this artery could not be sacrificed in order to split the medial surface of parenchyma so that the renal pelvis could be exposed Because of marked friability of the stricture, associated with marked inflammatory reaction of this area, it was felt that an intubation type procedure would not succeed

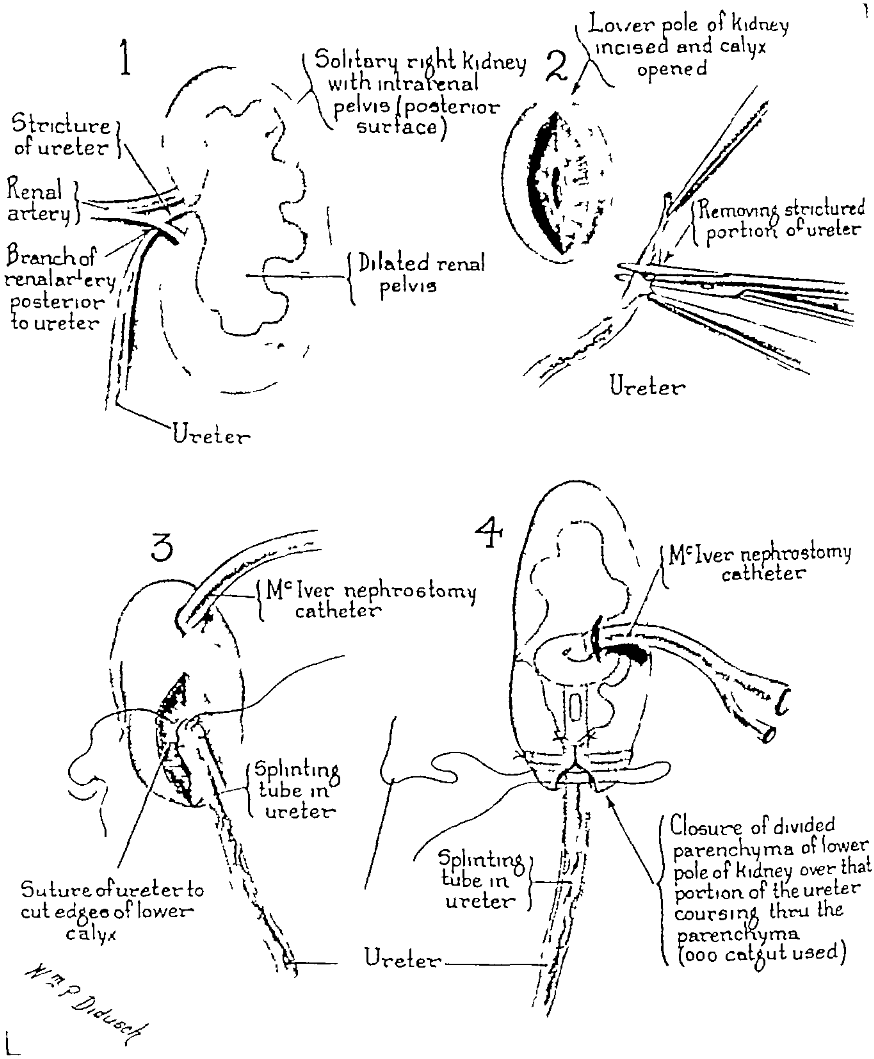
1
Stricture of ureter
Renal artery
Branch of renal artery posterior to ureter
Ureter
Solitary right kidney with intrarenal pelvis (posterior surface)
Dilated renal pelvis
2
Lower pole of kidney incised and calyx opened
Removing strictured portion of ureter
Ureter
3
McIver nephrostomy catheter
Splinting tube in ureter
Suture of ureter to cut edges of lower calyx
Ureter
4
McIver nephrostomy catheter
Splinting tube in ureter
Closure of divided parenchyma of lower pole of kidney over that portion of the ureter coursing thru the parenchyma (000 catgut used)
W. P. Didusch

FIG 2 Findings and procedure at time of first operation The mistake made was closur of lower pole nephrostomy over that portion of ureter coursing through it, later resultin in compression of ureter by fibrosis and contracture of parenchyma In retrospect, lowe pole amputation at site of ureterocalyceal anastomosis should have been performed

Rather than do a nephrostomy, which certainly would have been permanent, the decision was made to divide the ureter and approximate the free end to the lower calyx With a Doyen clamp on the renal vessels, the lower pole of the kidney was divided on the convex surface down to the lower calyx The lowe calyx was opened large enough to have a circumference about twice the size the circumference of the ureter The strictured and friable portion of urete was excised, after which a No 18 McIver nephrostomy tube with 12F splint wa brought through the kidney into opening of lower calyx The splinting portio of this catheter was introduced into the ureter, after which the upper free edg of the ureter was sutured to the mucous membrane of the calyx with 3 interrupted sutures of 4-0 chromic catgut Whether to amputate the lower pole of kidney up to site of anastomosis or whether to close the lower pole of kidney over that portion of ureter coursing through the parenchyma was debated, and it was felt that in all probability a better anastomosis could be obtained by closing the parenchyma over the ureter Therefore, several mattress sutures of 3-0 chromic catgut were taken through the parenchyma closing the nephrostomy of the lower pole of the kidney over that portion of the ureter coursing through it A rubber drain was left down to the kidney, after which the wound was closed in the usual manner

The patient tolerated the procedure very well, and postoperative course was essentially uneventful There was considerable urinary drainage by way of the tissue drain onto the dressing, but a major portion of urine drained satisfactorily through the nephrostomy tube The patient was discharged from the hospital on the tenth postoperative day and followed as an outpatient

The nephrostomy tube was removed on the twenty-second postoperative day and an excretory urogram made on the twenty-third postoperative day (fig 3, *A*) This pyelogram revealed essentially no change from the excretory urogram made prior to surgery It was felt that in all probability there was either compression of ureter by renal parenchyma, or else a stricture was forming at site of anastomosis

Following removal of the nephrostomy tube, the patient began to have low grade fever and pyuria which continued in spite of specific chemotherapy and antibiotics as indicated by urine culture and sensitivity tests

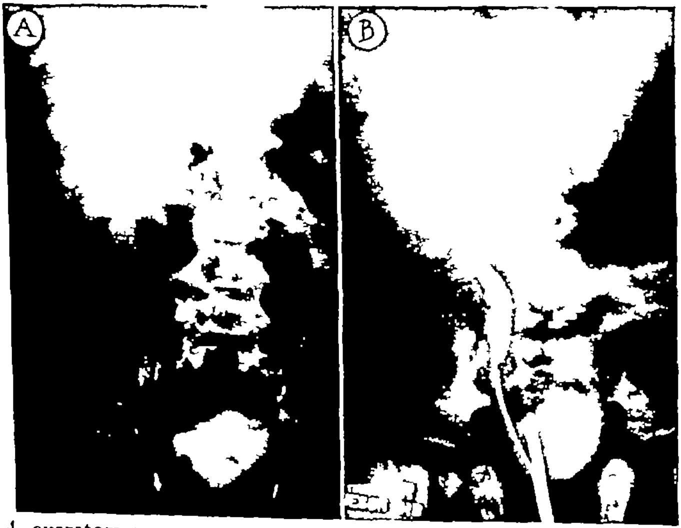

FIG 3 *A* excretory urogram on twenty third postoperative day Essentially no change from preoperative film *B* retrograde ureterogram on thirty second postoperative day Note filling of ureter up to point where ureter enters renal parenchyma At this point there is no evidence of contrast medium because of compression of ureter by fibrosis and contracture of lower pole of kidney

On the thirty-second postoperative day cystoscopy was performed and a 4F catheter was introduced into ureter and ureterogram made (fig 3, *B*), revealing compression of that portion of ureter coursing through the parenchyma The catheter was passed into the renal pelvis and left indwelling 36 hours During this time the patient became afebrile After removal of the catheter, the low grade fever promptly reappeared in spite of continued antibiotics and chemotherapy

On the thirty-ninth postoperative day, cystoscopy was repeated and a 5F catheter introduced to renal pelvis and left indwelling for 48 hours Again, during a period of ureteral catheter drainage there was no elevation of temperature, but low grade fever promptly reappeared upon removal of the catheter

Low grade fever and pyuria continued until the sixtieth postoperative day, at which time cystoscopy was repeated and a 6F catheter introduced into the renal pelvis with no difficulty Twenty-five cubic centimeters of grossly infected residual urine were obtained from the pelvis The catheter was left indwelling in order to decompress the kidney completely The patient was readmitted to the hospital and antibiotics and chemotherapy were continued The patient became completely afebrile in 48 hours

Second operation (fig 4) On the sixty-second postoperative day, the patient was taken to the operating room and the right kidney exposed The ureter was identified and freed by sharp and blunt dissection from point of exit from lower pole of kidney down to a point about 5 cm distally The lower pole of the kidney was found to be markedly scarred, indurated, and contracted from previous surgery and infection The lower pole was excised using sharp dissection, care being taken to leave the ureter intact at the site of anastomosis to the lower calyx The infundibulum of the lower calyx was opened and a right angle clamp introduced through calyx into upper ureter, with no evidence whatsoever of stricture at the site of the previous anastomosis It was then obvious that impaired drainage following the first operation resulted from fibrosis and contracture of lower pole parenchyma and compressed that portion of the ureter coursing through it The ureter was divided completely from the calyx, and the opening into the calyx was made larger by extending it into the infundibulum The entire fibrotic and contracted lower pole was amputated Using curved nephrostomy hook, a 14F polyvinyl catheter was brought through the convex surface of upper portion of kidney into the intrarenal pelvis and out the lower calyx and infundibulum A longitudinal incision was made on the posterior surface of the ureter for a distance of about 1 5 cm , and a similar incision made on the anterior surface of the ureter for a distance of about 2 0 cm After making several holes in that portion of catheter which was to be left in renal pelvis, the distal portion of the catheter was introduced into the ureter The free edges of ureter were sutured to the mucous membrane of the calyx and infundibulum with interrupted sutures of 4-0 chromic catgut No attempt was made to make a water tight closure After completion of anastomosis, a rubber drain was left down to the kidney and the wound closed in layers in the usual manner

The patient tolerated this procedure well and was returned to room in good

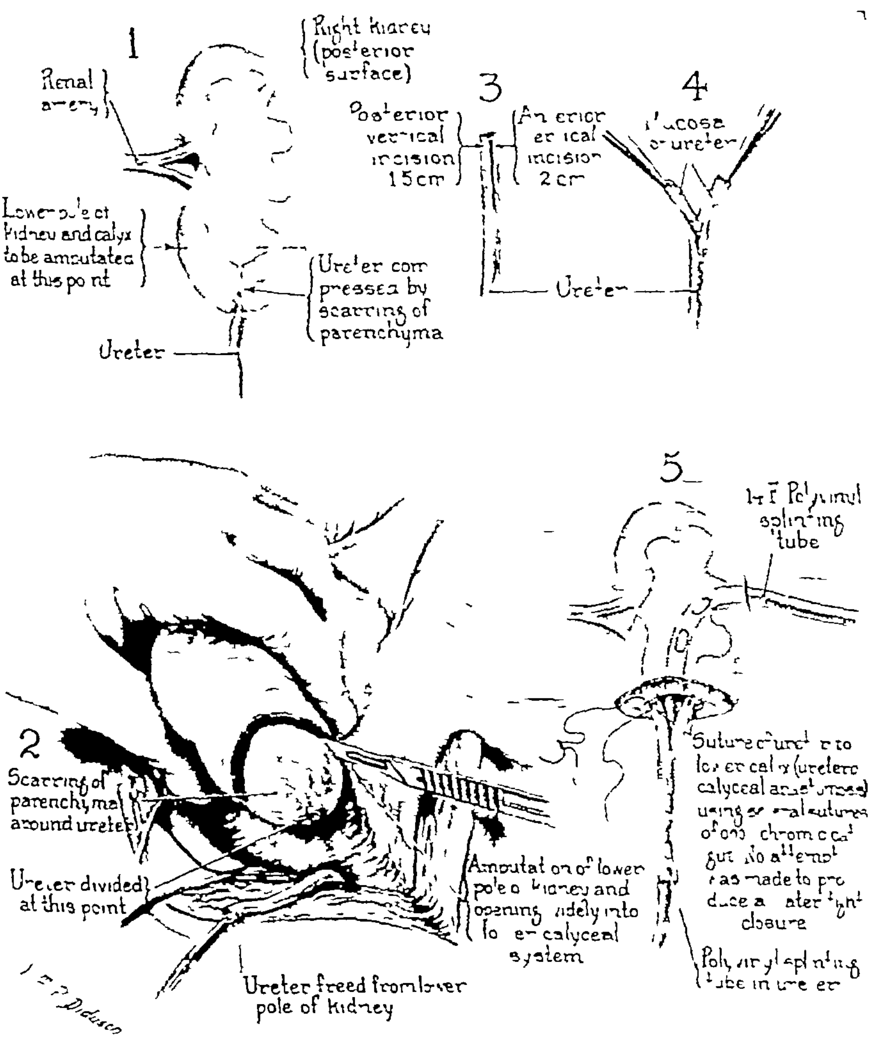
1
Right kidney (posterior surface)
Renal artery
Lower pole of kidney and calyx to be amputated at this point
Ureter compressed by scarring of parenchyma
Ureter
3
Posterior vertical incision 1.5 cm
Anterior vertical incision 2 cm
4
Mucosa of ureter
Ureter
5
14F Polyvinyl splinting tube
Suture of ureter to lower calyx (ureterocalyceal anastomosis) using several sutures of 000 chromic catgut No attempt was made to produce a water tight closure
Polyvinyl splinting tube in ureter
2
Scarring of parenchyma around ureter
Ureter divided at this point
Ureter freed from lower pole of kidney
Amputation of lower pole of kidney and opening widely into lower calyceal system

Fig 4 Findings and procedure at time of second operation Lower pole of kidney was fibrotic and contracted Amputation of lower pole with revision of ureterocalyostomy was performed

condition He was continued on antibiotics and other supportive therapy The convalescence was most satisfactory and again uneventful, and patient was discharged on tenth postoperative day

There was considerable urinary drainage onto the dressing for 15–20 days, but this soon became minimal The polyvinyl splint was removed on the thirty-sixth postoperative day, being replaced with a 12F nephrostomy tube A pyelogram was made through this nephrostomy tube on the fifty-ninth postoperative day (fig 5, 4) The nephrostomy tube was removed on the sixty-third postoperative day There was no urinary drainage from the flank following removal

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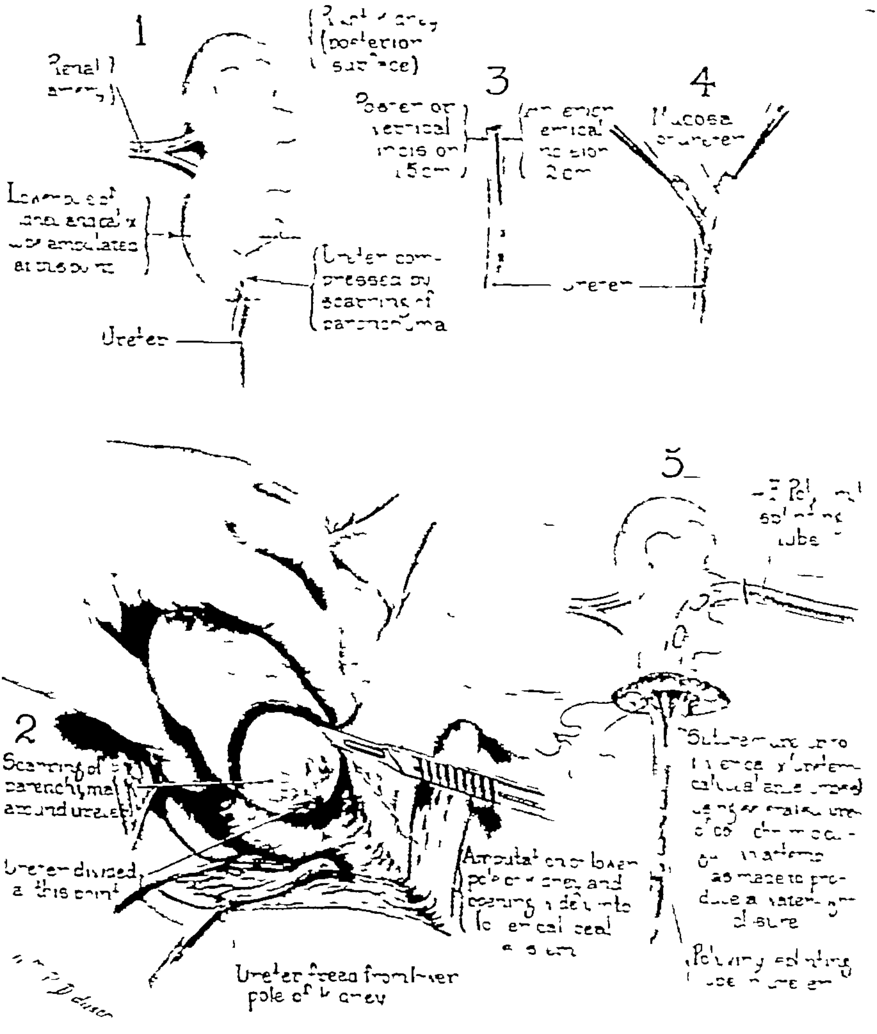
1
Renal artery (posterior surface)
Renal artery
Lower pole and calyx were amputated at this point
Ureter compressed by scarring of parenchyma
Ureter
3
Posterior vertical incision 1.5 cm
Anterior vertical incision 2 cm
Ureter
4
Mucosa sutured
2
Scarring of parenchyma around ureter
Ureter divided at this point
Ureter freed from lower pole of kidney
5
Polyvinyl splinting tube
Polyvinyl splinting tube in ureter

Fig. 4. Findings and procedure at time of second operation. Lower pole of kidney was fibrotic and contracted. Amputation of lower pole with revision of ureterocalyostomy was performed.

condition. He was continued on antibiotics and other supportive therapy. The convalescence was most satisfactory and again uneventful, and patient was discharged on tenth postoperative day.

There was considerable urinary drainage onto the dressing for 15–20 days, but this soon became minimal. The polyvinyl splint was removed on the thirty-sixth postoperative day, being replaced with a 12F nephrostomy tube. A pyelogram was made through this nephrostomy tube on the fifty-ninth postoperative day (fig. 5, A). The nephrostomy tube was removed on the sixty-third postoperative day. There was no urinary drainage from the flank following removal

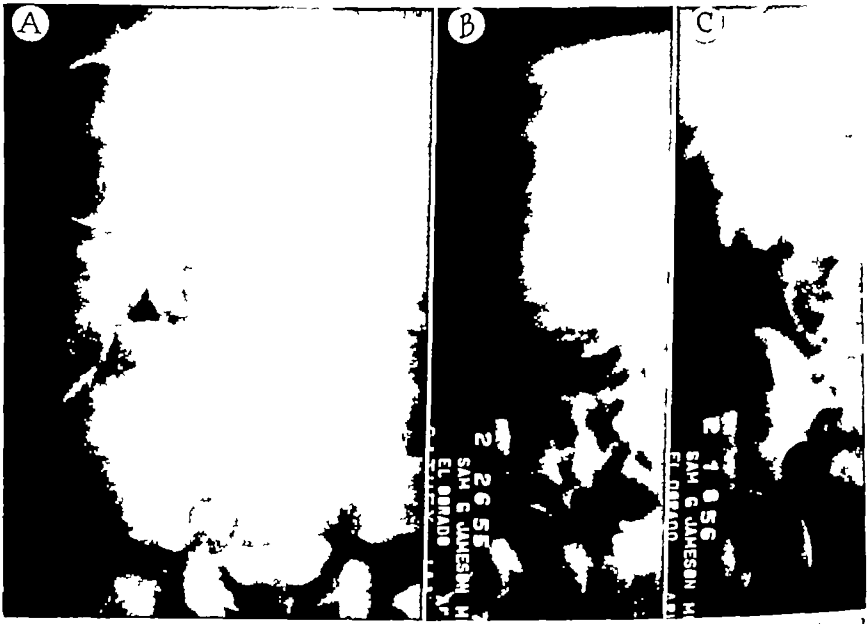

Fig 5 *A*, pyelogram made through nephrostomy tube on fifty-ninth postoperative day No evidence of extravasation of contrast medium at site of anastomosis, indicating complete epithelization at site of anastomosis *B*, preoperative excretory urogram and 9 month postoperative excretory urogram Note decrease of hydronephrosis

of the tube, and the nephrostomy site healed promptly Excretory urogram was made 9 months postoperatively (fig 5, *C*)

The patient has remained afebrile since removing the nephrostomy tube, and the urine has become negative He has continued to do extremely well in general, and at this time is completely asymptomatic

DISCUSSION

This patient has presented a multitude of problems First, the decision had to be made whether to do a nephrostomy in order to evacuate the uric acid crystals from the renal pelvis, or whether conservative therapy in the form of an indwelling ureteral catheter with alkaline irrigations would suffice The latter was found to be most satisfactory and is recommended as treatment of choice for this particular trouble

Second, at time of the first operative procedure the ureter was found to enter renal parenchyma without any evidence whatsoever of pelvis being located externally The upper ureter, because of friability and inflammatory reaction, was certainly not the ideal type tissue with which to do a successful pyelo ureteroplasty Longitudinal incision of the ureter into the renal parenchyma and renal pelvis was considered, with intubation over a prolonged period of time However, the marked amount of inflammatory reaction, along with the large aberrant renal artery, made this in the opinion of the authors, doomed from the onset In lieu of doing a nephrostomy, which certainly would have been permanent and progressively fatal, it was felt that ureterocalyostomy should be given a chance The error made at the first operation was the closing of that portion of the parenchyma through which the ureter coursed, resulting in compression externally of the ureter by fibrosis and contracture If the lower pole had been amputated up to the opening of the lower calyx at time of the first operation, it is believed that the ureterocalyostomy would have been successful from the onset

Third at time of second operation, the lower pole had to be amputated in order to release compression of that portion of ureter coursing through it Slightly more renal tissue had to be removed at this procedure than would have had to be removed if the lower pole had been amputated at the first operation In other words if this particular procedure is used in the future, the amount of kidney tissue which would be sacrificed by lower pole amputation would be much less than that which was amputated in this particular case

Fourth, as evidenced by the prolonged nephrostomy drainage even though the ureter was patent, there was temporary loss of peristalsis of the ureter, including both the frequency of peristaltic waves and the amplitude of each wave Swenson[1, 2] has done much investigative work on ureteral peristalsis, and because of his reports considerable confidence was obtained that the ureter would eventually regain its peristaltic properties This was evidenced several weeks later by the fact that the bladder output became more and more, and the output through the nephrostomy tube became less and less, even with the nephrostomy tube being left open continuously

Last, the authors are most cognizant of the fact that one case or one operation proves nothing However, because ureteropelvic stricture associated with a complete intrarenal pelvis is not too common, because there is no specific operative procedure designed for this type anomaly, and because in this particular case our end results were most satisfactory, we believe that our experience with lower pole amputation and ureterocalyostomy may well be of benefit to others who encounter this type anomaly It is for this reason that this one-case report has been prepared

SUMMARY

A case of congenital stricture with complete blockage of the ureteropelvic junction is presented This case was complicated by absence of the opposite kidney the presence of a complete intrarenal pelvis, and the coursing of a large aberrant artery posterior to the ureter

A method of dissolution of uric acid crystals in the ureter and renal pelvis is presented

A technique of lower pole amputation of the kidney with ureterocalyostomy is presented, and is recommended as the procedure of choice in the presence of hydronephrosis secondary to ureteropelvic stricture associated with a complete intrarenal pelvis

El Dorado Ark (S G J and J S McK)
Magnolia Ark (J F R)

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[1] Swenson Orvar and Marchant Douglas Ureteropelvic obstruction in infants and children J Urol 73 945–950 1955

Swenson Orvar Personal communications, 1955

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UNILATERAL URETERAL OBSTRUCTION AS SOLE MANIFESTATION OF ENDOMETRIOSIS

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The term, endometriosis refers to the occurrence of endometrial-like tissue in locations other than the uterus The theories of pathogenesis include that of Sampson which explains the disease as spillage from the uterine lining Others have explained endometriosis as metaplastic in origin while a third group states that embryonic rests are responsible [1]

ANATOMIC INCIDENCE

Vesical The bladder is the most commonly involved organ of the urinary structures, usually through direct extension from the contiguous pelvic endometriosis. Indicating the great possibility of confusing such vesical lesions with other pelvic conditions, O'Conor and Greenhill noted that of 58 patients with vesical endometriosis collected from the literature, 35 had had previous pelvic surgery [2]

Urethral Urethral endometriosis occurs rarely The appearance is that of a urethral polyp [3]

Renal Renal endometriosis is extremely rare and has been explained as due to mullerian inclusion in the metanephros [4]

Ureteral Endometriosis of the ureter may occur as bilateral involvement in advanced pelvic endometriosis or it may be a unilateral involvement in patients with little evidence of disease otherwise It is with the latter group that we are primarily concerned Ureteral obstruction from endometriosis is usually seen as the involvement of the ureter in a scar caused by overlying peritoneal disease, but there may be endometrial tissue protruding into the lumen of the ureter Randall termed this latter type "endometrioma of the ureter" [5]

DIAGNOSIS

A diagnosis of ureteral obstruction caused by endometriosis is difficult in cases not already massively involved by pelvic disease The conditions requiring differentiation include 1) those diseases associated with the urinary organs, such as ureterocele, congenital stenosis of the ureteral orifice, ureteral polyps, ureteritis cystica, inflammatory stricture of the ureter, nonopaque calculus and pelvic kidney, 2) other conditions arising in adjacent organs or areas involving the ureter, for example, malignant tumors of the ovary, uterus and broad ligament,

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Read at annual meeting of Western Section of American Urological Association, San Francisco, Calif April 30–May 3, 1956

[1] Boyd, William Textbook of Pathology Philadelphia Lea and Febiger, 1953, pp 696–698

[2] O'Conor, V J and Greenhill, J P Surg, Gynec & Obst, 80 113, 1945

[3] Goodall, J R Ann Surg, 120 891, 1944

[4] Marshall, V F J Urol, 50 652, 1943

[5] Randall, A J Urol, 46 419, 1941

retroperitoneal sarcomas, uterine leiomyomas and "Krukenberg" tumor Vesical endometriosis may have many of the features of ureteral endometriosis

SYMPTOMS

The symptoms may consist of those of ureteral obstruction alone, endometriosis alone or features of both It is when the urinary symptoms occur cyclically with some part of the menstrual cycle that the true nature of the disease may be most readily suspected Pain on the affected side is almost always present and may be lumbar, loin, or anterior lower quadrant It is usually of considerable years' duration historically Hematuria has been present in over one-half the cases and may be cyclical in those patients with invasion of the ureteral lumen Chills, fever, dysuria and frequency are manifestations of the accompanying urinary infection Dysmenorrhea, menorrhagia, and pelvic pain are features of the endometriosis Most of the symptoms of this condition would be expected to abate at menopause

PHYSICAL FINDINGS

The physical findings may include a palpable kidney associated with tenderness over the lower ureter in a woman with nodulation in the pelvis and posterior cul-de-sac Most of these women have the scars of previous pelvic operations

LABORATORY

Pyuria and microscopic hematuria are frequent laboratory findings The leukocyte count and differential smear may or may not be indicative of acute infection

X-RAY

The roentgenographic features are those of obstruction in the lower third of the ureter In the case of endometrioma of the lumen a filling defect can be seen on the ureterogram Excretory urography may show any degree of function or of upper tract dilatation

CYSTOSCOPY AND URETHROSCOPY

Endoscopy is of value in demonstrating the presence or absence of endometriosis of the urethra or bladder Endometrioma of the bladder is manifested by typical "chocolate" cyst appearance which increases at the time of the menses Whether the vesical lesion is typical or not, biopsy is a practical means of identification Vesical endometriosis has produced ureteral obstruction by involving the orifice [6]

TREATMENT

The treatment of this condition should be designed to correct the localized obstruction of the urinary tract and to prevent the effects of endometriosis elsewhere in the body The treatment of endometriosis is castration, either by surgical, x-ray or hormonal means Bilateral oophorectomy is the most certain method but x-ray and male hormone therapy have also been successful [7] Four cases of ureteral obstruction have been treated by castration alone In three of them the affected kidney was improved or became normal [8]

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[6] Williams G A Urol & Cutan Rev , 47 554, 1943

[7] Navratil E Wien klin Wochnschr 58 6641, 1946

[8] Ratliff R K and Crenshaw W B Surg , Gynec & Obst , 100 414, 1955

There is no reported case of a woman in the menopausal group with ureteral obstruction due to endometriosis who had been followed by urograms to determine the fate of the kidney There is no reported case treated by local excision of the obstruction alone (except by nephroureterectomy), although vesical endometriosis has been treated by local excision, with poor results generally, in the hope of sparing relatively young women the other effects of the menopause In the case which we are presenting surgical castration and local excision were combined to produce a good result

Endometriosis obstructing one ureter has been previously reported eight times It is the purpose of this paper to add a ninth case to the literature

CASE REPORT

Miss M C O'L, a 50-year-old white woman, was admitted to the hospital on April 14, 1955, complaining of chills, fever and left lower quadrant pain at intervals of about 6 months for a 3-year period During the last episode, 3 months prior to admission, she had total, gross hematuria on one occasion She was referred to a urologist who performed an excretory urogram which showed left hydronephrosis The patient had an appendectomy at the age of 9 and the removal of a cervical polyp at the age of 38 She had dysmenorrhea until age 40 but there had been none since that time Her menstrual cycle was entirely normal and regular

Physical examination showed a woman who appeared younger than 50 years of age Blood pressure was 130/76 mm of mercury, the temperature and pulse were

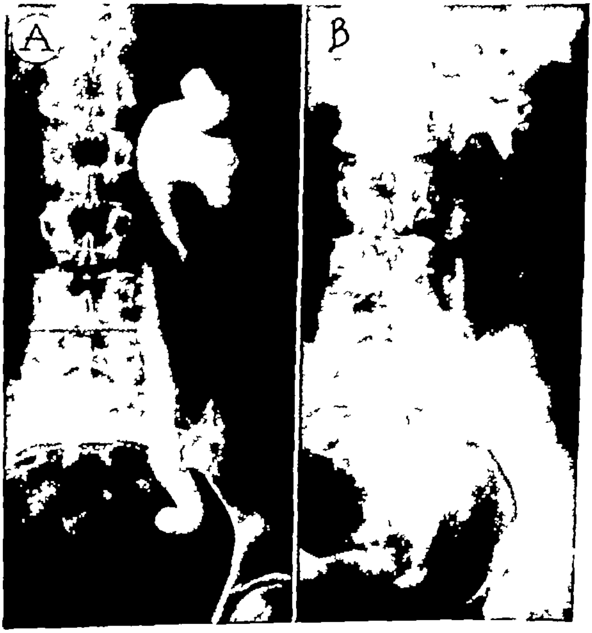

Fig 1 A, left hydronephrosis and hydroureter to level of third sacral segment (retrograde pyeloureterogram) B, pyeloureterogram performed at time of withdrawal of splint (fourteenth postoperative day)

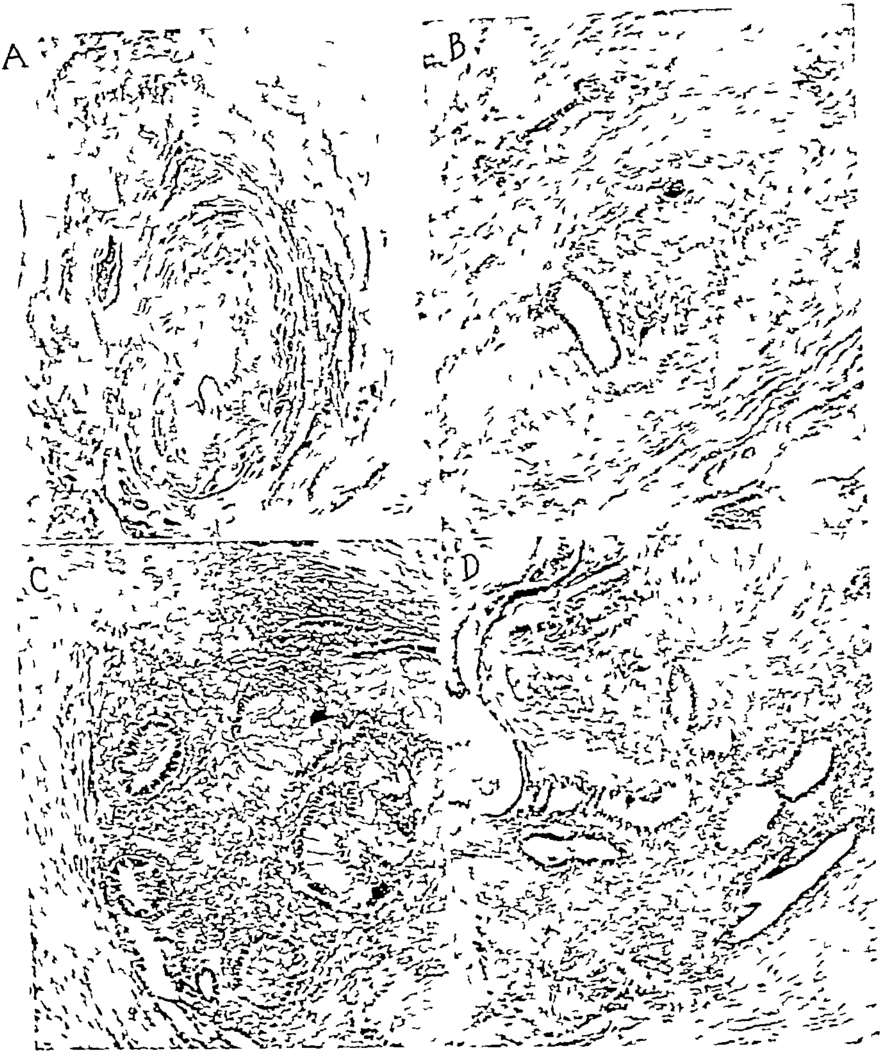

FIG 2 *A*, islands of endometrium in upper left periureteral area (low power) *B*, endometrial gland surrounded by small spindle cells resembling stroma (× 100) *C*, endometrial tissue invading round ligament (× 100) *D*, area of endometriosis in vesicovaginal area (× 100)

normal The positive findings were slight tenderness in the left lower quadrant on deep palpation and nodules in the posterior cul-de-sac on pelvic examination

On admission the hemoglobin was 13 6 gm /100 cc, white blood cells, 7,050 with a normal distribution on differential smear The hematocrit was 41 per cent and the erythrocytic sedimentation rate was 14 mm /1 hour Urinalysis showed a pH of 6 0, albumin and sugar, negative, microscopically, an occasional leukocyte and one to three epithelial cells were found per high power field Urine culture revealed no growth in 48 hours The blood urea nitrogen was 17 mg /100 ml X-ray of the chest and a barium study of the colon showed no abnormality Sigmoidoscopy demonstrated a normal rectum and lower sigmoid colon An excretory urogram showed prompt bilateral function and left hydronephrosis and hydroureter to the level of the third sacral segment Cystoscopy revealed a normal bladder A 5F ureteral catheter was passed to the left kidney pelvis and 55 cc clear urine aspirated which proved to be sterile on culture Examination of this urine for malignant cells disclosed none A left retrograde pyelogram and ureterogram showed the same findings as the excretory urogram with little drainage on the 45-minute delayed film (fig 1, *A*)

At surgery on June 6, 1955, the left hydroureter was found to be bound down by scarred periureteral tissue with very adherent overlying left adnexal organs and peritoneum This tissue was bluish-black in color and on frozen section was diagnosed endometriosis A firm, irregular nodule removed subperitoneally in the right posterior cul-de-sac was also diagnosed endometriosis A total hysterectomy and bilateral oophorectomy were performed The dilated left ureter was freed up and found to be of sufficient length for reimplantation The scarred area was resected and the distal ureter excised The bladder was opened, a hemostat was passed through the left ureteral orifice and the dilated ureter pulled into the bladder where its splayed end was fixed internally and externally with interrupted chromic No 0000 sutures A 10F polyethylene tube was used as a ureteral splint, being brought out through the urethra

Pathological description (We are indebted to Dr John H Rowe, Department of Pathology, for the following details of the gross and microscopic findings) The gross specimen consisted of a total uterus with attached fallopian tubes and ovaries The uterus was nodular in appearance with multiple, subserosal myomas The uterus measured 12 by 8 by 7 cm and weighed 190 gm The peritoneal sur

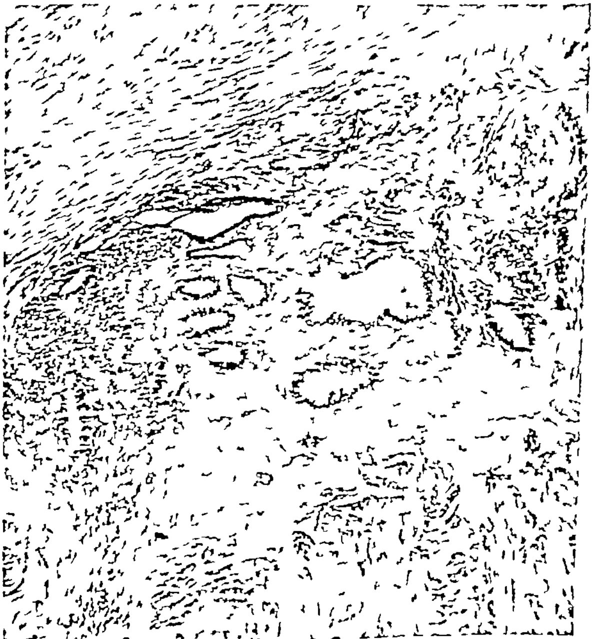

FIG 3 Portion of endometrial tissue compressing left ureter (× 100)

face of the fallopian tubes and ovaries was red and hemorrhagic The fallopian tubes measured 7 cm. in length and the ovaries each measured 3 cm in greatest diameter On cut section of the uterus the endocervical canal was patent and the endometrium did not appear remarkable Cut section of the ovaries revealed multiple, small, hemorrhagic cysts

Several small, firm segments of fibrous tissue from the region of the round ligament, right vesicovaginal region and from the left periureteral tissue, including a small section of ureter, were submitted with the main specimen

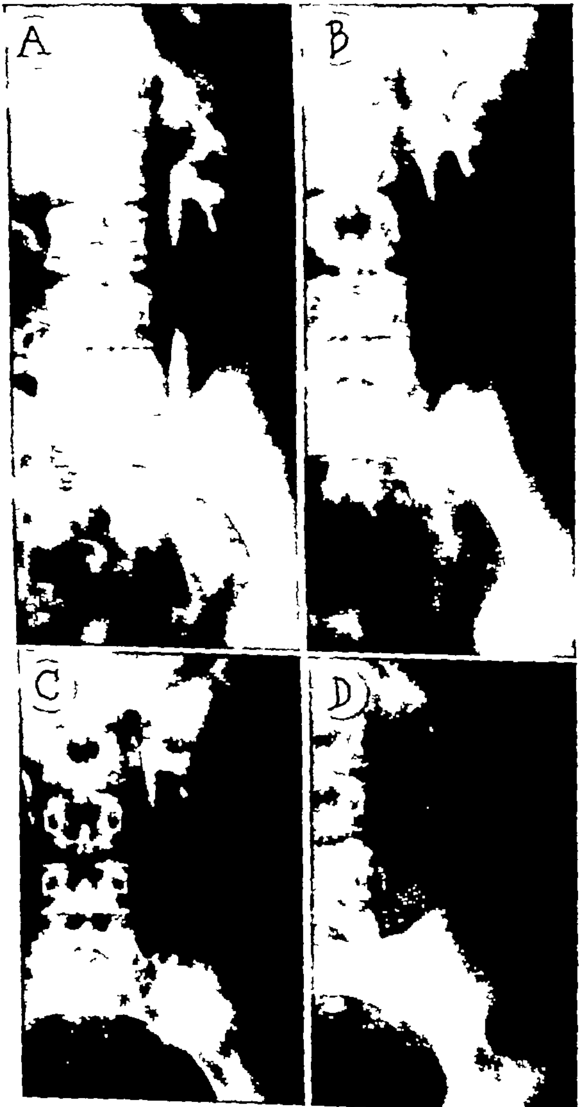

Fig 4 *A* excretory urogram 15 minute film 3 weeks postoperatively *B*, 20 minute upright film showing satisfactory drainage of dye *C* excretory urogram 15-minute film, 6 months postoperatively indicating good function and lack of hydronephrosis *D*, 20-minute upright film showing satisfactory drainage

Microscopic examination Sections of the uterus revealed multiple myomas with no evidence of endometrial invasion of the myometrium Sections of the ovaries revealed multiple follicular cysts, corpus luteum cysts and a single hemorrhagic corpus luteum No areas of endometriosis were seen in the ovaries

A section of ureter revealed small islands of endometrium in the periureteral fibrous tissue (fig 2, *A*) High power examination of these areas revealed small glands lined by cuboidal epithelium surrounded by small spindle cells resembling endometrial stroma (fig 2, *B*)

Islands of endometrial tissue were found in the tissue removed from the round ligament (fig 2, *C*), from the right vesicovaginal region (fig 2, *D*) and from the tissue surrounding and compressing the left ureter (fig 3)

The immediate postoperative course was uneventful On the fourteenth postoperative day a retrograde pyeloureterogram was performed, utilizing the tubular polyethylene splint which was withdrawn The pyelogram was normal while the ureterogram showed dilatation but good drainage (fig 1, *B*)

One week later an excretory urogram showed a normal pyelogram and good drainage from the dilated ureter (fig 4, *A* and *B*) Two months postoperatively an 8F Braasch bulb catheter passed easily to the left kidney An excretory urogram 6 months after surgery (fig 4, *B* and *C*) showed normal calyceal, pelvic and ureteral structures bilaterally A catheterized bladder urine specimen showed gamma streptococci on subculture Microscopically, the centrifuged urine showed 1 to 2 leukocytes per high power field The patient was entirely well and had no menopausal symptoms

COMMENTS

Randall observed in reporting the first case of ureteral obstruction due to endometriosis that this condition was rare but probably not so rare as the paucity of recognition would indicate This comment is doubtless still valid

Our reported case, as well as those of other writers, demonstrates that this unusual complication of a common disease can be completely cured if a diagnosis is made early and the relatively simple procedures of castration accomplished Since our patient is the only one with excision of the affected portion of the ureter and reimplantation of the proximal segment into the bladder, we cannot predict what success this procedure may have in other instances It has been most satisfactory in this single case

SUMMARY

Unilateral ureteral obstruction occurred in a 50-year-old woman as a result of paraureteral and ureteral scar formation incident to pelvic endometriosis No cyclical manifestations of the disease could be elicited Therapy consisted of excision of the affected portion of the ureter and reimplantation into the bladder with reversion of the obstructed kidney and ureter to normal status This is the ninth reported case of unilateral obstruction of the ureter due to endometriosis and the only one treated by local excision and ureterocystostomy

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COMPLICATIONS DUE TO USE OF THE JOHNSON URETERAL STONE BASKET

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Although the Johnson stone basket is a widely accepted and useful instrument for extraction of small calculi from the lower third of the ureter, its use may not be without penalty in some cases. Beneventi and Creighton (1955) reported inability to remove the instrument on one occasion, with the necessity for subsequent transvesical ureterotomy to free the basket. Middleton and Grau (1952) found it necessary to deliver an impacted basket and the contained stone from the ureter by considerable traction under anesthesia. Rusche and Bacon (1940), who recorded numerous cases of ureteral trauma, did not mention this complication.

Recently we have observed 2 cases in which the stone basket became impacted in the lower ureter. This complication and ensuing events seem worthy of report in brief detail.

CASE REPORTS

Case 1. W. V. A. No. 54771, H. J., a 59-year-old man, experienced left lower quadrant pain intermittently for 7 weeks. During that time a ureteral calculus 8 mm. in diameter had failed to move from a point 4 cm. above the left ureteral orifice. A Johnson basket was passed and the stone engaged, but the basket could not be delivered through the ureterovesical junction. After 5 days of intermittent traction, left flank pain and fever necessitated surgery. A transvesical meatotomy was done and the instrument removed. The end result is a stricture of the intramural ureter with ureteral and pelvicalyceal dilatation. See figure 1.

Case 2. H. H. No. 40605, J. H., a 44-year-old asthmatic man, complained of right flank pain. A calculus approximately 1.0 cm. in diameter was present in the upper ureter. Five days later the stone was arrested in the lower ureter. Because of abdominal distention and vomiting, the basket was passed and the stone engaged. However, the instrument could not be withdrawn through the ureteral orifice. A roentgenogram showed clearly that the stone protruded from the confines of the instrument (fig. 2). After 2 days of intermittent traction, the basket was removed under general anesthesia. To the operator's dismay two-thirds of the calculus remained in the ureter, necessitating extravesical ureterotomy. At surgery the ureter was edematous. Despite a stormy convalescence, the

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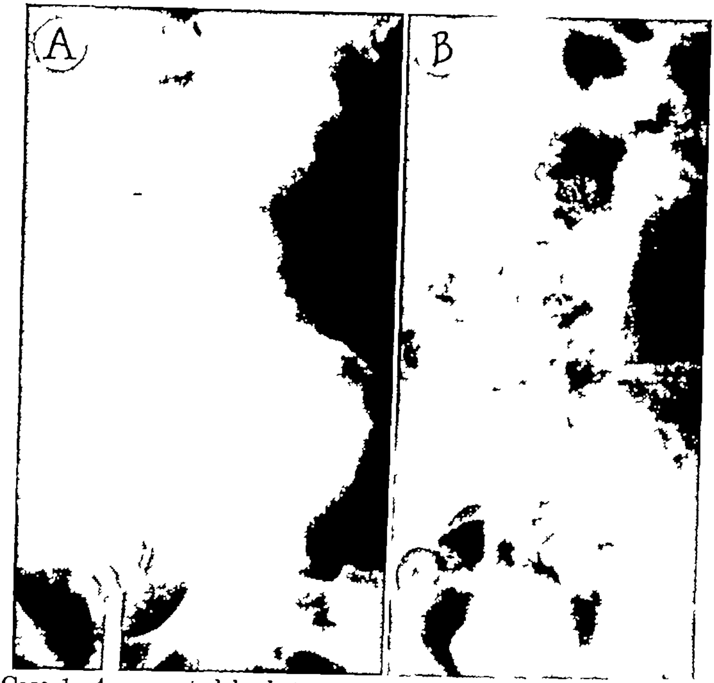

Fig 1 Case 1 *A*, impacted basket containing calculus *B*, urogram 3 months post operatively Note ureteral and pelviocalyceal dilatation

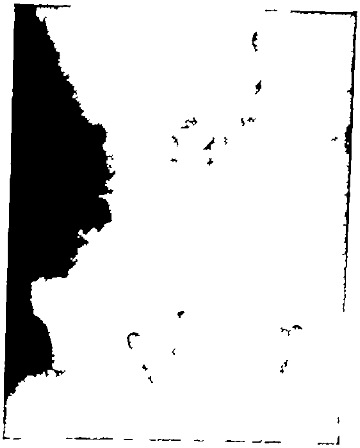

Fig 2 Case 2 Note stone that protrudes from basket

patient is well The excretory urogram is normal, but there is a 2 cm stricture contiguous with the right ureteral orifice

SUMMARY

Two cases are reported in which the Johnson ureteral stone basket became impacted in the lower ureter necessitating operative removal

CONCLUSION

The Johnson stone basket is most useful when a ureteral calculus lies in the lower third of the ureter and is less than 5 mm in diameter Its use in other areas of the ureter or in patients with larger calculi may be dangerous

Ureteral meatotomy seems clearly indicated prior to passing a Johnson stone basket in cases where the ureteral orifice is small or contracted

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EXPERIMENTAL METHODS OF URETERONEOCYSTOSTOMY EXPERIENCES WITH THE URETERAL INTUSSUSCEPTION TO PRODUCE A NIPPLE OR VALVE

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When surgical necessity dictates reimplantation of the normal or abnormal ureter into the bladder or bowel, the surgeon is faced with the probability of creating or perpetuating an abnormal situation vesicoureteral reflux This sometimes serious complication may allow recurrent pyelonephritis, hydronephrosis, hydroureter, calculus formation, renal acidosis, and uremia In those instances where vesicoureteral reflux is not the primary problem, as in reimplantation of the ureter after resection of bladder tumors, the various tunneling procedures have proven highly successful, even though they may allow reflux The major, and still unsolved problem is found in those cases, almost all children, where primary reflux causes infection and progressive renal damage This situation has occupied the attention of many recent workers Hutch (1952) devised an operation to imbed the ureter in the bladder wall without severing its normal connection This has been most successful in paraplegics, but results are not predictable in other cases Mathisen (1953) utilized the valve principle in ureterointestinal anastomosis, constructing a "nipple" from the bowel wall With increasing intraluminal pressure, the nipple is supposed to close and prevent reflux Gallo (1951) described a technique, used in ureterointestinal anastomosis, in which a "nipple" is formed from the terminal ureter and sutured so that it lies within the bowel lumen He claims good results and prevention of reflux in 48 cases Monod and Van Verts (1908) illustrated a similar method of making an ureteral nipple for reimplantation of the ureter into the bladder

Vest and Parke Smith have independently utilized this idea in the reimplantation of the ureter into the bladder Their early results were encouraging A recent experimental study by Hill, Dodson, and Hooper (1955) confirms the clinical work of Vest and Parke Smith, and indicates the difficulty of doing this type of ureteroneocystostomy in dogs Edelbrock's excellent article (1955) on ureterovesical obstruction mentions this "cuff technique of Vest " It is his belief that reflux, while not desirable, is not always injurious to the kidney Swenson, Fisher and Cendron (1956) have recently reported their experience with the use of isolated ileal segments to replace ureters and prevent reflux in children with megaloureters by utilizing the active peristalsis of the ileum We have used ileal segments successfully to replace portions of damaged ureters in adults and know that it is technically feasible Perhaps, encouraged by Swenson's optimism, we shall employ this procedure in selected cases to prevent reflux in children

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Read at annual meeting of Western Section of American Urological Association, San Francisco, Calif April 30–May 3, 1956

EXPERIMENTAL WORK

Because the problem of preventing vesicoureteral reflux is not yet solved, the work described below was carried out to study ureteroneocystostomy in laboratory animals

Method Nine adult dogs were used, four male and five female Later in the experiment, four puppies were used in an attempt to produce more favorable conditions for the experiment

A suprapubic, transperitoneal incision was used The ureters were identified and cut free as they entered the bladder The bladder was opened in its dome and a clamp was pushed through the bladder from within and spread widely near the original ureteral orifice The cut end of the ureter was led into the bladder On one side, the ureter was anastomosed to the bladder after first making a cuff by rolling the ureter back on itself On the other side, a direct anastomosis of ureter to bladder mucosa was performed, after first splitting the ureter to make a fishmouth At the time of surgery in this first experiment, the anastomoses appeared unsatisfactory due to the very small caliber of the ureters This dog died of peritonitis within 24 hours

Because of this first complete failure, it was felt that an attempt should be made to produce a hydroureter before attempting reimplantation For this reason, subsequent experiments were done in two stages At the first stage, the ureter was partially occluded by tying it with black silk over a No 20 needle as it entered the bladder At a second stage, in seven to ten days, the suprapubic incision was reopened and the hydroureters identified and transected as they entered the bladder When the ureters were dilated, it was much easier to form the cuff by rolling the ureter back on itself, so that the subsequent nipple or cuff measured one centimeter in length as it projected into the bladder The anastomoses were accomplished with interrupted 4-0 chromic catgut sutures, suturing the entire thickness of the ureter to the bladder mucosa on the inside and fixing the serosa of the ureter to the outside of the bladder to relieve all tension on the primary suture line Because of early difficulties with extravasation, we made an effort to establish good bladder drainage in the immediate postoperative period This was done in male dogs by suturing in place a suprapubic tube that was cut off flush with the skin In female dogs, a catheter was inserted through the urethra from the bladder side and sutured to the inside of the bladder and then cut off just outside the urethral meatus After the dogs had survived both procedures, cystograms and excretory urograms were performed to evaluate the urinary tract Finally, the surviving dogs were sacrificed

In a separate series of experiments, four puppies were used They had a suprapubic operation with exposure and partial ligation of the vesical neck in an attempt to produce partial urinary retention and dilatation of the upper urinary tract, so that the nipple operation might be attempted

Results Of nine adult dogs, three were lost, four died as a direct result of surgery and only two survived for complete evaluation (table 1) Three months after the second operation, dog A died of peritonitis, due to leakage of urine at the ureterovesical junction on the side of the direct anastomosis The kidney and

TABLE 1 *Results of animal experiments*

	Cystogram	IVP
Dogs		
3 lost to followup		
4 died as result of surgery (dog A lived 3 months)	No reflux	
2 survived and sacrificed (dog B, 11 months)	No reflux	Hydronephrosis on side of direct anastomosis
(Dog C, 10 months)	Reflux on side of direct anastomosis	Normal
Puppies		
4 died as result of surgery		

ureter on this side showed dilatation and evidence of extensive infection On the side of the cuff anastomosis, the ureter and kidney were normal One month following the second operation, a cystogram showed no reflux on either side

Dog B was observed for 11 months A cystogram showed no reflux on either side, but the excretory urogram showed hydronephrosis on the side of direct anastomosis When this animal was sacrificed, the bladder, ureters, and kidneys were removed in one mass The ureter on the side of the direct anastomosis was dilated three times, and the kidney was small and contracted with parenchymal scars (fig 1) The ureter and kidney on the side of the cuff procedure were normal On manual compression of the distended bladder, marked reflux was noted up the side of direct anastomosis None was seen on the cuff side With the bladder

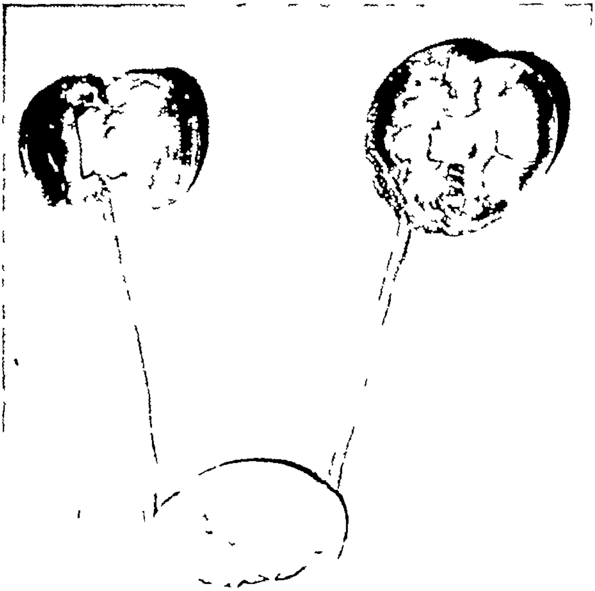

FIG 1 Dog B Note dilated right ureter, contracted right kidney, and well formed nipple at left ureterovesical junction

open, the direct anastomosis of the ureter to the bladder was well healed and wide open On the cuff side a healthy-appearing 1 cm nipple of ureter projected into the bladder and accepted a No 5 ureteral catheter with ease

Dog C survived for 10 months before sacrifice Cystography showed reflux to the kidney on the side of the direct anastomosis, but the excretory urogram was normal without evidence of hydronephrosis This animal was sacrificed and the urinary tract was removed in one mass The ureter and kidney on the side of the direct anastomosis were normal, except for minimal dilatation of the lower half of the ureter The ureter and kidney on the side of the cuff procedure were normal On manual compression of the distended bladder, there was obvious reflux up the ureter on the side of the direct anastomosis and none up the side of the cuff procedure When the bladder was opened, the direct anastomosis and the nipple both appeared healthy The intravesical nipple measured one centimeter, and its lumen accepted a No 5 ureteral catheter (fig 2)

Four puppies subjected to partial ligation of the vesical neck did not fare so well They all died as a result of surgery, and no hydronephrosis or hydroureter was detected at autopsy A better way to induce chronic obstruction would be the use of cellophane to produce progressive occlusion of the urethra

Summary of animal experiments The foregoing experimental work turned out to be most disappointing from the standpoint of helping us to decide about the actual value of the cuff or nipple operation in the prevention of vesicoureteral reflux The one certain thing learned was that surgery on the bladder and lower

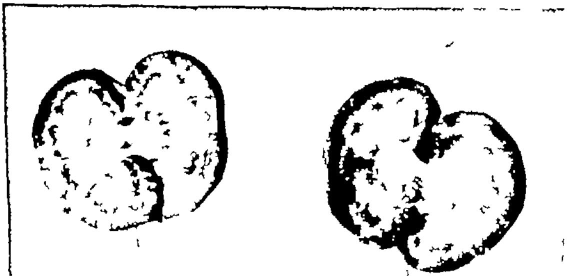

FIG 2 Dog C Note normal kidneys and ureters, and well formed nipple at left ureterovesical junction

ureter in the dog is made difficult by the fact that the bladder is an intraperitoneal organ With inadequate drainage methods, one almost invariably has extravasation, peritonitis, and death The two dogs that survived indicate that the cuff is feasible and will give a properly functioning ureterovesical junction without reflux or stricture formation It is doubtful if this good result is reproducible 100 per cent of the time The unpredictability of results is emphasized in the clinical trials of Vest and others, who have not enjoyed unfailing success

CLINICAL EXPERIENCES

After hearing of Vest's early results, the nipple type of ureteral implantation was tried in November 1954 in a child with congenital absence of the abdominal muscles and bilateral vesicoureteral reflux The operation was technically satisfactory, but failed to prevent reflux, probably due to the extremely dilated ureters He has been maintained since with a permanent cystostomy tube

Our thoughts turned to other possible ways of preventing vesicoureteral reflux

Intussusception The idea of ureteral intussusception to produce a valve presented itself G I Smith and Hinman (1955) successfully employed an intussusception technique to produce a valve in an isolated loop of ileum, and Eiseman (1953) used this same principle in producing venous valves experimentally in the vena cava Silen and McCorkle (1956) have tried it experimentally in the aorta Because of their encouraging results, and the above unfavorable clinical experience with the nipple or cuff operation, it was decided to utilize an intussusception type of procedure to attempt to form an intraluminal ureteral valve-like action near the bladder

Technique The actual technique for production of this ureteral intussusception follows directly from operations for production of the nipple or cuff (fig 3)

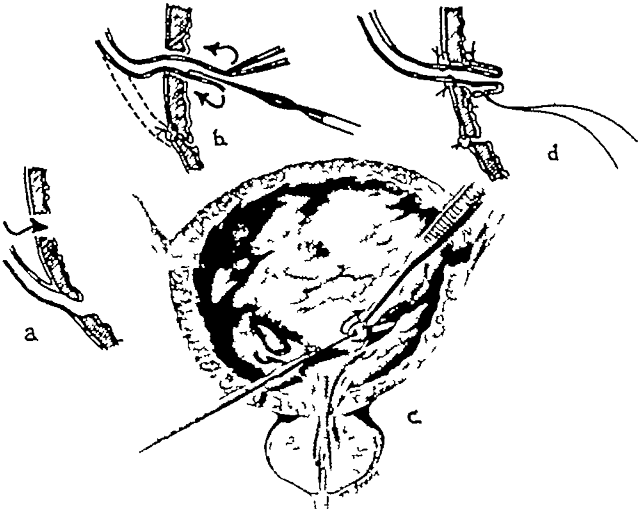

Fig 3 Production of "nipple of Vest" performing true ureteroneocystostomy

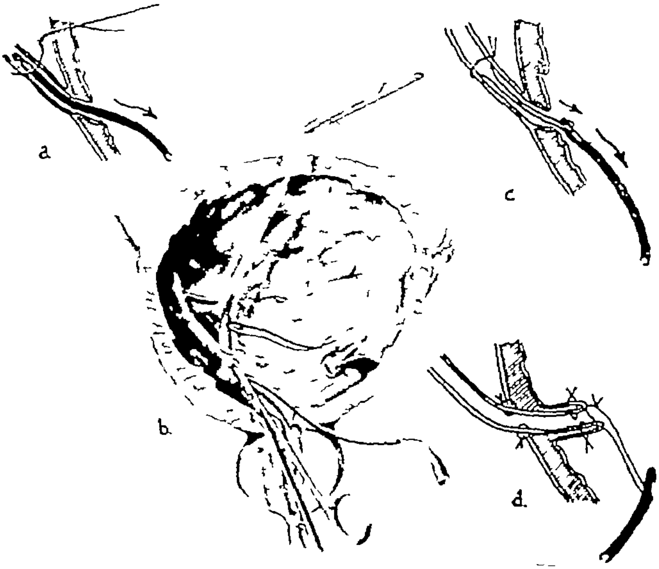

FIG 4 Production of "nipple of Vest" in situ

Vest completely severed the ureter as it entered the bladder and then produced a cuff by folding the cut end of ureter back on itself and then reanastomosing it to the bladder

The same cuff-like orifice may be produced "in situ" by a slightly different technique (fig 4) The ureter is left attached to the bladder and meatotomy is performed when indicated The lower ureter is freed transvesically, so that, with the aid of an indwelling ureteral catheter, it can be intussuscepted into itself and into the bladder, suturing it in place to produce a nipple Hodges (1956) has recently utilized this independently with good early results in 7 patients

A valve-like intussusception of the ureter may be produced just outside the bladder (fig 5)

More of the ureter is pulled into the bladder so that when the ureter is reduced, it carries with it the nipple, which now in effect becomes a valve outside the bladder

The production of a ureteral valve by intussusception has been used in two clinical cases to date, with interesting and equivocal results The actual surgical production of this valve at first seemed difficult because we are dealing with abnormally thin ureteral walls It should be noted that this principle and surgical procedure seem applicable only to the dilated ureter

The ureteral orifices are approached transvesically and catheterized The lower end of each ureter is then approached through an incision in the back of the bladder (fig 5) The technical problem of producing ureteral intussusception in this area has been solved by the following maneuver suggested by one of us (P T) After the lower segment of ureter is partially freed, a rubber ureteral catheter is inserted and a suture is placed through the ureteral wall and the catheter The catheter is then pulled down, leading the suture into the bladder

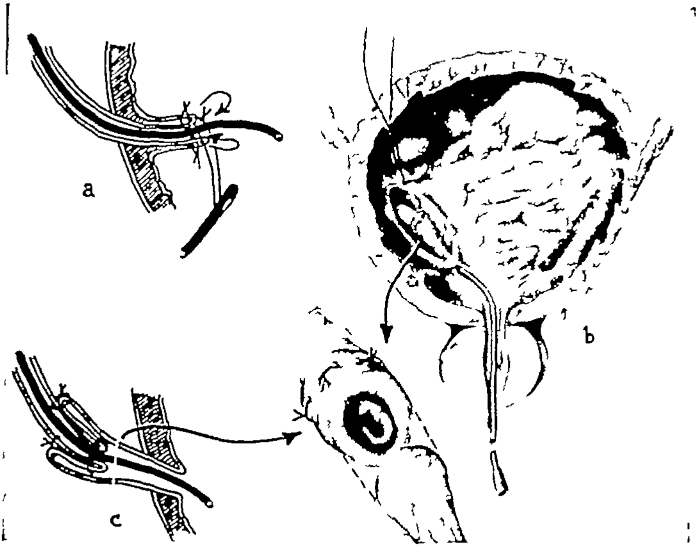

FIG 5 Production of ureteral valve by intussusception

The silk suture is loosely tied on the outside of the ureter, and firm traction causes effective ureteral intussusception Catgut sutures are then placed through the two layers of the ureteral wall, so that this partial intussusception will remain fixed during healing and become permanent The silk traction suture is removed The ureter is then pulled back out of the bladder carrying with it the intussuscepted portion, which now is, in effect, a ureteral valve (fig 5) These valves were splinted with ureteral catheters which were brought out through the suprapubic wound and left in place for approximately 14 days

CASE REPORTS

G H (University Hospital No 011-02-41) A 6-year-old boy had urinary infection and fever 5 months before entry to the hospital A urological study revealed bilateral hydronephrosis and hydroureter, worse on the left side There was bilateral vesicoureteral reflux (fig 6, *A*) There was no apparent obstruction at the vesical neck at the time of cystoscopy Neurological examination was normal

On October 4, 1955, a suprapubic exploration of the bladder was accomplished A Bradford Young type of revision of the vesical neck was done, in spite of the fact that there was no obvious evidence of obstruction Both ureters were explored transvesically as described above, and valves were created bilaterally by the intussusception technique (fig 5)

Postoperative course was satisfactory and the catheters were removed on the fourteenth postoperative day A week later a cystogram showed no reflux He was readmitted about 6 weeks later for a second excretory urogram and a cystogram At this time, reflux was demonstrated on the left side, but none on the right Excretory urography showed improvement in both upper urinary tracts He was healthy and happy

At cystoscopy it was possible to look into the dilated ureteral orifices and

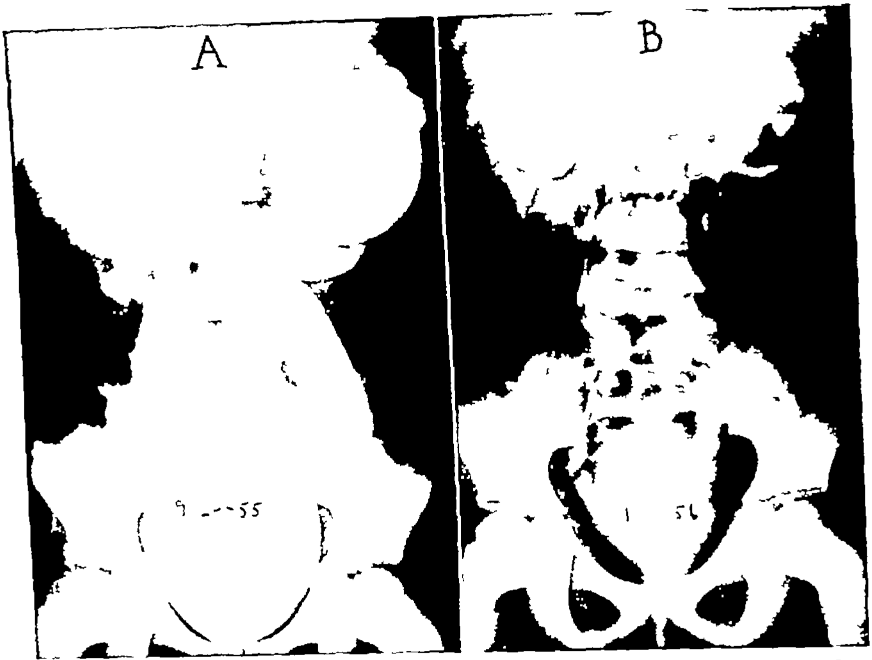

FIG 6 *A*, Preoperative cystogram on G H Note bilateral vesicoureteral reflux *B* postoperative excretory urogram on G H Note valves at lower end of each ureter

observe the valves in situ This was particularly effective on the left side, which had been so remarkably dilated It was possible to pass the No 16 McCarthy instrument through the dilated ureteral orifice upward into the ureter to the region of the valve, which could be seen as a kind of a diaphragm "winking" at the operator It was not completely patent, but it seemed to act in a circular constricting fashion as the ureter contracted

The appearance of this valve was very striking indeed

The child was observed again in January 1956, three months postoperatively Excretory urograms showed considerable improvement (fig 6, *B*) and it was possible to identify the ureteral valves on each side The urine was sterile and he was able, by "double voiding," to empty his bladder A cystogram showed reflux up both sides, but not so much as formerly The right side seemed to be better than the left

He has not been followed long enough for a definitive statement or evaluation concerning the ultimate result It would seem from these early studies that at least the situation has not been made any worse The role of the Bradford Young vesical neck plastic operation cannot be assessed although it is quite evident that this alone may have accounted for the improvement in the upper urinary tract

S S (University Hospital No 011-57-52), a 4½-year-old boy, was admitted to the hospital in December 1955 with bilateral nephrostomy tubes in place The history revealed that the child had had previous surgery consisting of cystostomy when an acutely obstructive bladder was noted about a year earlier He had later undergone bilateral nephrostomies and a transurethral resection of the vesical neck Preliminary x-ray studies showed evidence of ureterovesical obstruction due to a narrowing just outside the bladder (? Chwalla's valves)

On December 30, 1955, essentially the same procedure as that described above in case 1 was accomplished In this case, however, it was found that the ureters were obstructed where they entered the bladder Ureteral meatotomy was done, after the perivesical portion of the ureter had been well mobilized, and meatotomy was carried up through a definite area of valve-like formation in the lower ureter This undoubtedly represented Chwalla's valve on each side and the ureter was markedly dilated above it When these dilated ureters were to be reimplanted in the bladder, it became evident that there would obviously be reflux and accordingly the intussusception type of valve was made in the lower ureter on each side as described in case 1

There was also a marked hypertrophy of the trigone which was acting as a veil-like obstruction to the middle portion of the bladder This was treated by clamping both sides of it and cutting between clamps dividing the base of the bladder in the obstructive area The previous prostatic resection had cleanly removed any evidence of obstructing prostatic tissue or vesical neck obstruction

His postoperative course was unremarkable and he was discharged with his nephrostomy tubes still in place Followup excretory urograms were satisfactory, but some evidence of retention of dye persisted in the upper tracts However, when he was in the erect position, this was considerably improved, and he was able, by "double voiding," to get out most of the residual dye There still seemed to be reflux, particularly on the right side

At followup cystoscopy on a later admission, a polypoid excrescence seen in the region of the right valve was looped off and found to be granulation tissue On the left side, the reimplantation had produced an overgrowth of vesical epithelium in such a way that a kind of a veil was formed over the ureteral orifice, which now was very narrow and would barely admit a No 5 ureteral catheter X-rays showed bilateral reflux, worse on the right

In his case, the valves did not seem to function as such, and did not seem to prevent reflux However, he is still under observation to see what the long term results of his case will be

SUMMARY

The background of operations for reimplantation of the ureters and prevention of vesicoureteral reflux is reviewed Experiences with animal experimental material, in which reimplantation of the ureter into the bladder of dogs was studied, are reported Results with the simple reimplantation and the "nipple" or "cuff" type of implantation are described

The early results of clinical experiences with an intussusception type of operation to create a valve in the ureter just outside the bladder are described in 2 cases The method of intussuscepting the ureter to form either a nipple or cuff in the bladder or an extravesical valve is described and illustrated in detail

CONCLUSIONS

Ureterovesical anastomosis with various attempts to prevent reflux is difficult to perform in dogs Early results in the only 2 animals surviving out of thirteen suggest that the "nipple" or "cuff" technique may protect the kidney when compared with the simple direct anastomosis

Ureteral intussusception is an easy and practical method for forming a "valve or cuff or nipple" at the ureterovesical junction The technique of intussusception may be modified to produce a "valve-like" structure in the lower ureter just outside the bladder In the present studies, this valve does not prevent reflux, but it does seem to impede it somewhat without causing upper urinary tract obstruction Further clinical studies attempting to discover the most practical and effective method for preventing ureteral reflux are indicated The problem is not yet solved

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URETERAL REGENERATION EXPERIMENTAL AND CLINICAL

PART II

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Rapid strides are being made in our knowledge of the behavior of the ureter following extensive injury, but we have yet to learn the effect of this regeneration upon the kidney which is dependent upon ureteral function for adequate emptying We know that large defects of the ureter can be bridged The components of the wall will be anatomically replaced with minor variations of appearance in a minimum of 6 weeks What we do not know is exactly how the kidney reacts to this damage and regeneration, nor do we know whether an altered response may be partially responsible for some of the less favorable operative results It was again necessary to take our problem to the laboratory in search of an answer and it is, therefore, the purpose of this experiment to 1) observe the status of the kidney proximal to the regenerated area of the ureter and 2) to study the regenerated segment in regard to the anatomical picture, type of peristalsis and nerve regeneration

Material and method A total of twenty-four large (over forty pounds) dogs were divided into 3 groups These were anesthetized with intravenous pentobarbital sodium following which an intravenous urogram was obtained by injecting 20 cc of 70 per cent urokon sodium * A left subcostal incision was then made transecting the flank muscles thus exposing the kidney and ureter without difficulty The peritoneal cavity was usually not entered, but the opening, if made, was immediately closed tightly, and care was taken to separate the renal vessels from the peritoneal reflexion At a point 1 0 cm below the ureteropelvic junction, the ureter was then completely excised for a distance of 3 0 cm , except for a strip one to two mm wide A 3 to 5F polyethylene combined splint and nephrostomy tube was passed down the ureter for from 4 0 to 6 0 cm below the excised area while the proximal end was brought through the middle calyx of the kidney as a nephrostomy tube Care was taken at this point that the only size used would pass down the lumen of the ureter with perfect ease Two drainage holes were then cut in that portion of the tube which lay in the renal pelvis only, and the splint was, therefore, solid as it traversed the ureteral defect (fig 1) A light weight aluminum motion restricting collar was applied immediately and for 5 days the dogs were given 300,000 units of procaine penicillin† in each 24-hour period The surgical wounds were checked daily for infection and urine drainage if any, and the nephrostomy tubes were allowed to drain externally causing no difficulty The splinting-nephrostomy tube was removed on the sixth

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* Urokon sodium supplied by Mallinckrodt Co St Louis, Mo for use of this work

† Antibiotics were supplied by Chas Pfizer & Co New York, N Y for use in this work

postoperative week Fourteen to sixteen weeks later the animal was again anesthetized and a check intravenous urogram was made in the same manner as in the first operation The kidney and 8 0 cm of attached ureter were then removed Periureteral fibrosis was observed and graded from 1 to 3 on an arbitrary scale where grade 1 showed minimal adhesions and allowed blunt dissection of the ureter from its surrounding tissues Sections were then taken at four levels, namely, one below, and two through the excised area, one of which was a cross section and the other longitudinal Lastly a wedge-shaped section was taken of the kidney parenchyma Paraffin sections stained with hematoxylin and eosin were used for histological study

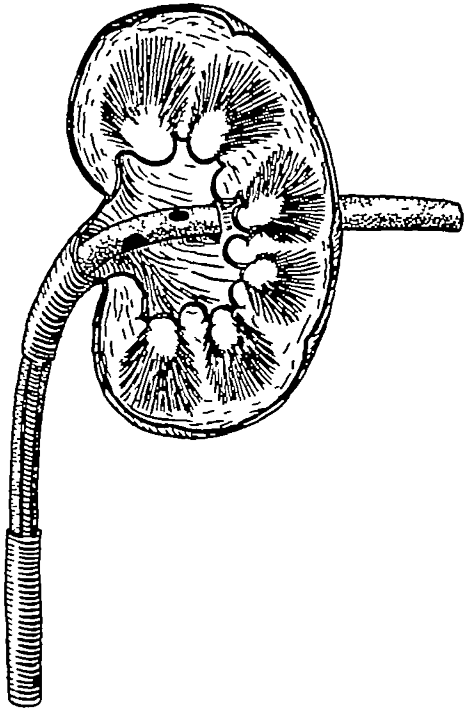


FIG 1 Schematic drawing of small combined nephrostomy and ureteral splint spanning excised segment

The second group of animals was treated in an identical manner as the preceding group with the exception that 12 weeks after the removal of the splint they were again anesthetized as before Through a longitudinal incision 0 5 cm long and 6 0 cm below the ureteropelvic junction, electrodes were introduced into the regenerated segment of the ureter and electromyographic and pressure transducer tracings were recorded Immediately following this, similar tracings were taken of the normal ureter below this area for control

The third group of dogs was treated as in the preceding groups except that 15 weeks after the removal of the splint a check excretory urogram was taken Four weeks later, under ether anesthesia, the affected kidney together with 6 0 cm of ureter was removed Longitudinal sections were taken of both the regenerated and normal areas of ureter These were immediately stained with the Sakovich modification of the methylene blue technique of nerve tissue

At the onset 2 dogs were operated upon by the identical technique used throughout this experiment except that the excised area was replaced with a tube of tantalum mesh gauze in which three longitudinal windows were cut and the tube placed around the polyethylene splint This was sutured with three interrupted No 80 cotton sutures to the proximal and distal cut ends of the excised area, thus holding the defect open for 3 0 cm The splint was removed at the usual sixth postoperative week Three weeks later at the second operation the kidney and 8 0 cm of the ureter were removed for examination The wire mesh was removed from the ureteral wall by sharp dissection and sections were taken both through and below the excised area for histological study Paraffin technique with hematoxylin and eosin stains was again used

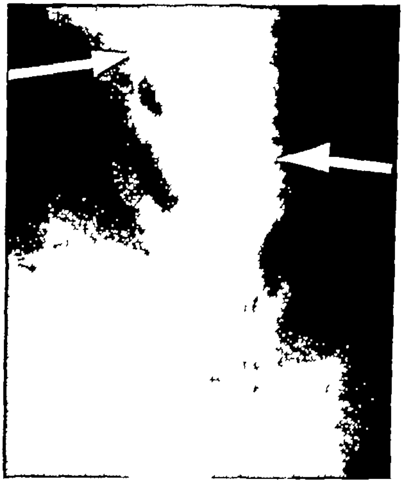


FIG 2 Excretory urogram 15 weeks following ureteral segmental excision Normal canine kidney, right, dilated, previously intubated kidney, left

Results of observations In all groups of animals representative preoperative excretory urograms showed that the normal unoperated canine kidney has a markedly intrarenal pelvis that empties rapidly making it frequently quite difficult to visualize However, 15 weeks following the excision of the ureteral segment the renal pelvis is dilated from one to three times its original size (fig 2) A moderately prolonged emptying time was observed accompanied by some concentration of dye, however, this was not a true hydronephrosis as the calyces retained their normal "cupping" appearance

Postoperative periureteral fibrosis was seen in all cases as would be expected, but in most instances it was less than originally anticipated The grading of the perirenal and periureteral fibrosis was of necessity an arbitrary measure, but 80 per cent of the specimens were grades 1 and 2 Nearly all of the ureters were seen to be strongly adherent to the lower pole of the kidney for a distance of 1 0 to 2 0 cm, but, there was no evidence of impairment of freedom of motion In regard to contributing factors to fibrosis such as urine drainage and infection, less than 5 per cent of the dogs had urine drainage from the wound and less than 10 per cent had wound infections It was also noted that the use of large or oversized splints produced very large amounts of hard periureteral and renal scar tissue associated with ureteral obstruction which was located at the distal end of the splint This produced urinary and renal parenchymal infection, pyonephrosis and a subsequently nonfunctioning kidney The gross appearance (fig 3) of the kidney where small splints were used varied but slightly from normal, while the lumen of the regenerated segment was one to two times larger in diameter The wall was softer to palpation, and the serosa irregular in outline in contrast to the smooth, symmetrical appearance of the normal The microscopic picture confirmed the original findings at 6 weeks following ureteral excision and showed a thinner mucosal layer and thinner muscular layers contrasted to the block-like appearance of the mature muscularis Inflammatory tissue was not a problem in this series as only 20 per cent of the animals showed any large amount of polymorphonuclear leukocytic or lymphocytic infiltration

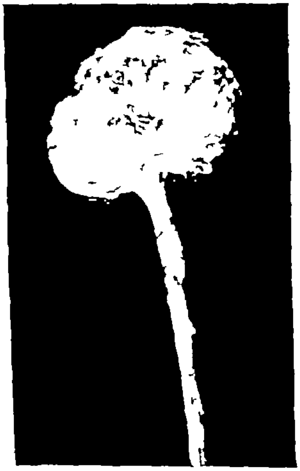
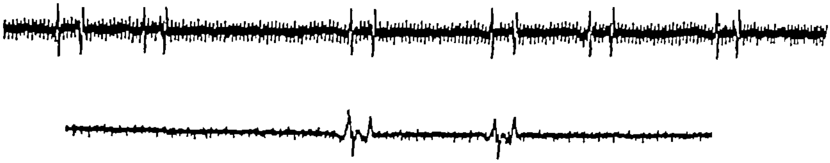
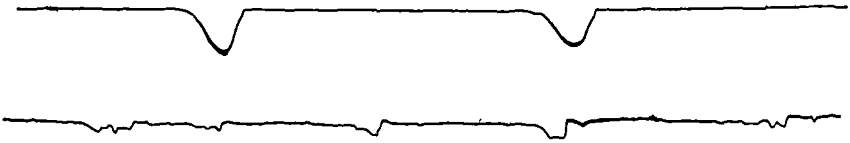


FIG 3 Gross appearance of canine kidney and ureter 15 weeks following ureteral segmental excision

In the second group of dogs which were used for study of ureteral peristalsis, it was found that electromyographic tracings of the normal ureter showed the same configuration as several other authors have recorded and may be considered as a normal tracing of the intact canine ureter Tracings taken of the regenerated segment, however, showed a different configuration (fig 4) with a wave which was lower with greater width than the normal The paper speed in both E M G tracings was constant at 1 0 cm per second It was found that with the electrodes each 25 mm distance the velocity of the peristaltic wave averaged 56 mm per second in the normal ureter, 25 0 mm per second in the regenerated segment This series is too small to make the calculations highly accurate, but the difference in the two peristaltic waves is apparent Recordings of the Gauer-Gemapp



E.M G. TRACINGS–ELECTRODES 25 mm DISTANCE–PAPER SPEED 1.0 cm/sec.
Line 1 Normal ureter
Line 2 Regenerated segment



PRESSURE TRANSDUCER TRACINGS–PAPER SPEED 0 5 cm/sec
Line 3 Normal ureter
Line 4 Regenerated segment

FIG 4

pressure transducer completed the picture of peristalsis by recording intraluminal pressure, this again showed a difference between the inverted cone-shape wave which was identical in occurrence and configuration in the normal, but roughly cone-shaped and only one half as deep in the regenerated segment

Nerve stains of the regenerated segments of the ureter show a heavy but fine lacework of nerve fibers as in the normal The fibers are of the same appearance when seen under the 16 mm microscopic lens, but quantitatively an estimated 20 per cent less (fig 5)

Following the removal of the splint, the intravenous urograms appeared much the same as those kidneys of regenerated segments without the interposition of the wire mesh The gross specimen showed no external evidence of this mesh, but it was found to be incorporated in the wall of the bridged gap which appeared the same as other regenerated areas Microscopically there was an increase in the fibrous and inflammatory elements, however, the picture was the one familiar to regeneration

Discussion It is established in the laboratory that the ureter regenerates large defects and functions, we further know that the bridged gap varies in 1) appearance both grossly and microscopically showing thinner structures of the muscularis and mucosal layers, 2) peristalsis is slower and the waves are of lower magnitude as measured by the electromyograph and pressure transducer Further 3) the nerve supply is less dense These factors reflect upon the kidney which continues to function well, but also varies from the normal by retaining a mild dilatation of the pelvis and calyces with a prolonged emptying time This altered appearance and function seems to be a permanent factor at least up to five months postoperatively The prolonged emptying of the kidney could possibly

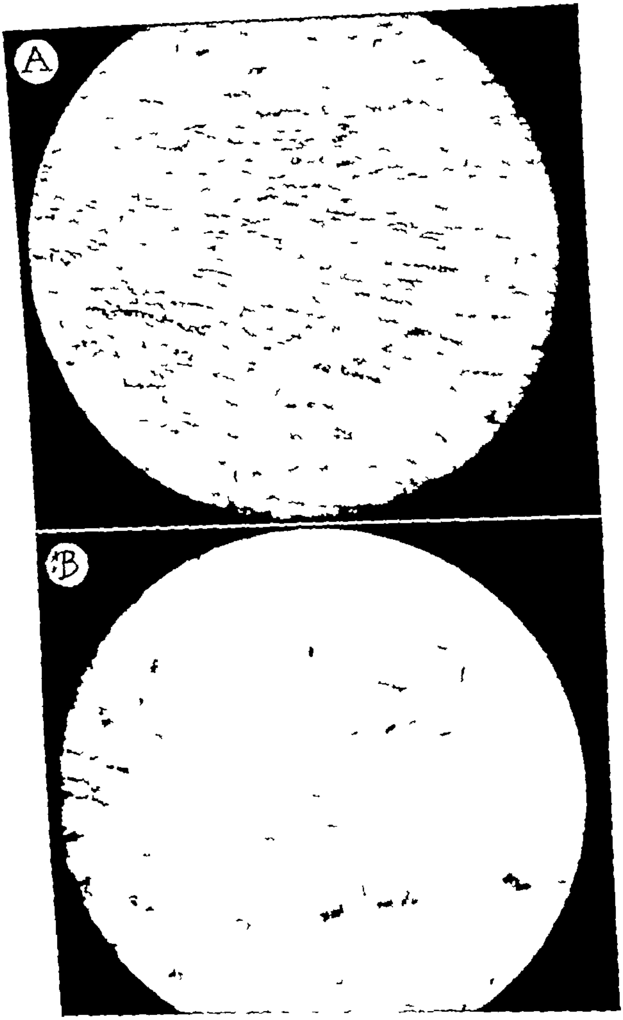


Fig 5 *A*, nerve stains of normal ureter *B*, nerve stains in regenerated ureter, decreased density noted in regenerated segment

be the result of moderately increased inflammatory elements in the ureteral wall or postoperative stricture However, these were not a problem as it has been seen that the regenerated segment maintained a larger lumen than the normal and 80 per cent of the cases showed periureteral fibrosis to be in grades 1 and 2 The mechanism of the altered functions is not yet clear, but knowledge has been gained that these phenomena do exist and do not cause any great impairment of function either experimentally or clinically, but must be investigated further

It was necessary at the onset of this work to see if the bridged ureteral defect was a true regeneration or a sliding together of the cut ends The fact that the mesh was incorporated in the wall in all probability indicates an actual regeneration The work of Oppenheimer and Hinman has proved this point and, further, that the repair is an actual regeneration of smooth muscle

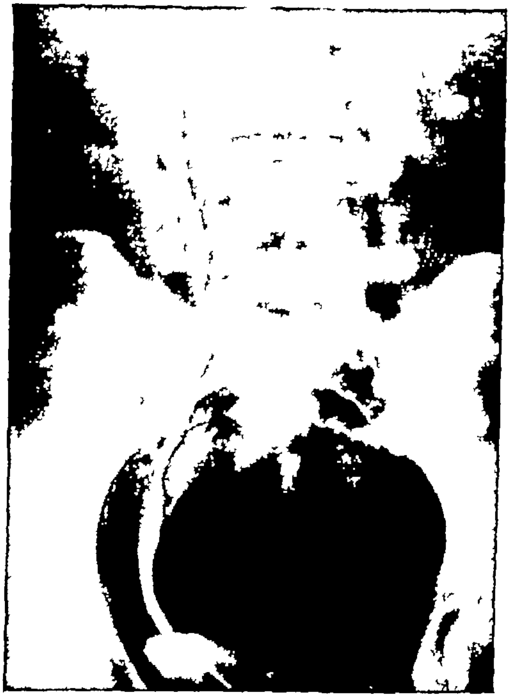


Fig 6 Retrograde ureterogram of severe stricture following use of 14F T tube at pyelo plasty Stricture 2 cm long caused grade 2 hydronephrosis

Clinically we know that all surgical repairs on large ureteral defects do not end with perfect appearance and function of the kidney Therefore, several questions arise

1) *How does the ureter respond functionally to a large defect?*

2) Although it regenerates smooth muscle and mucosa does it possess adequate peristalsis?

3) Will there be stricture formation and how can it be avoided?

4) How well does the kidney function after the removal of the splint?

It is now established that

1) The regenerated ureter functions adequately

2) Active peristalsis is present within the regenerated segment

3) Stricture formation is absent in the laboratory animal when small caliber splints are used, and present with large caliber splints

4) Even though the kidney retains a slight to moderate distention it apparently functions adequately

Clinical observations The technique of surgical repair of long strictures or injuries that require intubated ureterotomy is still unaltered from the basic precepts of nontraumatic surgery, a dependent position of the ureteropelvic junction, the removal of redundant pelvis, and the maintenance of the wound and regenerating segment free of urine leakage

Two main postoperative observations have been made namely, 1) that the retrograde ureterograms on many of the 6-month postoperative films showed a definite decrease in the caliber of the lumen of the bridged gap, and 2) without increased dilatation of the renal pelvis This apparently is not a true stricture as a No 10 bulb catheter can be passed to the kidney pelvis without evidence of obstruction This clinical phenomenon coincides accurately with the experimental findings in the laboratory Probably the most important observation was made in the laboratory where it was noted that the use of oversized ureteral splints produced an impassable stricture at a point below the regenerated area and coincided with the area opposite the tip of the splint This has been observed in several patients, one of whom required a secondary nephrectomy four years after the intubated ureterotomy when a very severe stricture developed following the use of a large "T" tube nephrostomy splint (fig 6) This fact, which was found both experimentally and clinically, has altered the technique to include only those splints which will pass down the ureter and require absolutely no pressure or trauma Other than this one factor the additional experimental information has caused no change in the technique of handling these cases as described in our previous work

SUMMARY

Following the repair of large ureteral defects, the kidney functions well, but has a reduced ability to empty and moderate dilatation of the pelvis and calyces

Experimentally, the regenerated segment shows moderate variations from the normal, namely, thinner laminae muscularis and mucosae, slower and less intense peristaltic waves and a decreased density of the nerve pattern

Large caliber or oversized splints produce marked fibrosis and severe ureteral stricture formation, whereas the small caliber splints give an adequate lumen and no stricture formation No change is indicated in the operative technique except the clinical use of small ureteral splints

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EXPERIENCES WITH URETEROINTESTINAL ANASTOMOSIS

DONALD C. MALCOLM

Completely satisfactory diversion of the urine after removal of the bladder has not been attained. Each of the methods of ureterointestinal or ureterocutaneous anastomosis is fraught with constriction or ascending infection or a combination of both of these deleterious incidents. Enthusiasm for cystectomy and attendant urinary diversion has fluctuated and varied in the individual performing such procedures as well as amongst his local, regional, national and even international colleagues. For a time rather vehement denunciation was leveled at those advocating such radical methods but improvement in surgical morbidity and mortality ameliorated this controversy. Great clarification was contributed by Jewett[1] in classifying the probability of cure, as related to penetration or infiltration of the vesical epithelium, after cystectomy for transitional epithelioma. Prior emphasis had been placed upon the anaplastic activity of the cells.

It became more evident that small mucosal epithelioma could be treated transurethrally. Recurrence in the area, related to depth of penetration from biopsy material, multiple recurrence or changing characteristics of the growth from a pedunculated to sessile type allowed for less rigidity in either dictating early cystectomy or persistent endoscopic or transvesical therapy.

Hinman and Weyrauch[2] surveyed the literature dealing with all methods of ureterointestinal anastomosis in 1936. These were segregated into eleven procedural principles. Most methods have courted safety from leakage and prevention of reflux by means of multiple sutures and tunneling, only to win constriction at the site, thus increasing renal infection and diminishing renal function. Nesbit[3] and Cordonnier[4] rather boldly sought for unimpeded drainage by incising the serosa, muscularis and mucosa of the colon with suture of the spatulated ureteral tip to the mucosa.

In 1950, Weyrauch,[5] independently of Woodruff and Leadbetter,[6] demonstrated the frequency of reflux from the colon via the ureter to the renal pelvis unless a preventative valve-like-mechanism was used (fig. 1). Their independent proposal reverted to the subserosal tunnel of the colon for the ureter to prevent reflux.

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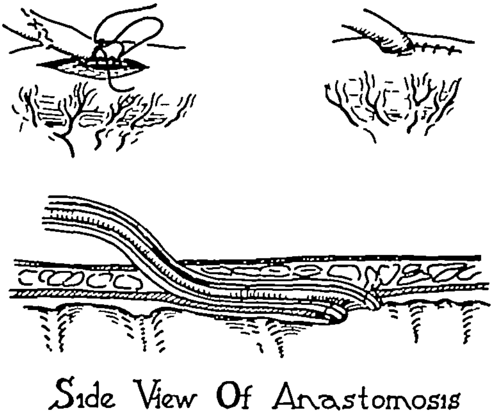

FIG 1 Weyrauch and Leadbetter combined anastomosis using submucosal tunnel and mucosa-to-mucosa suture of ureter to colon

TABLE 1 *Ureterocolic anastomosis (1946–1956)*

Method	Living	Result
Flocks, 3	3	Constricted Renal infection
Barnes, 6	5	Constricted Renal infection
Nesbit, 10	3	Most expired of neoplasm
Miscellaneous, 5	0	Expired of extensive neoplasm
Mathisen, 7	1	Expired of neoplasm Two died of serum hepatitis

Gilchrist and Merricks[7] utilized the distal segment of the ileum and ascending colon as a separate reservoir for urine Bricker[8] developed ureteral anastomosis with a segment of the ileum whose terminal portion opened directly on the abdomen It was developed chiefly for patients requiring extensive removal of the pelvic organs but has been used when only the bladder was extirpated

Creevy[9] has summarized the difficulties attending the atavistic reversion to the cloacal state as due to ascending infection, intracolonic pressure, constriction of the anastomosis and induction of acidosis Sinaiko[10] quotes various authors and their disappointments Lloyd and Baumrucker[11] stated that pyelonephritis was inevitable and ultimate in a high percentage regardless of technique utilized or the skill employed But they also stated that ureterocutaneous diversion resulted in constriction at or below the margin of skin, renal calculi and pyelonephritis with the additional esthetic objection of the patient wearing tubes or devices on the abdomen Lapides[12] found urographic abnormalities in 77 per cent

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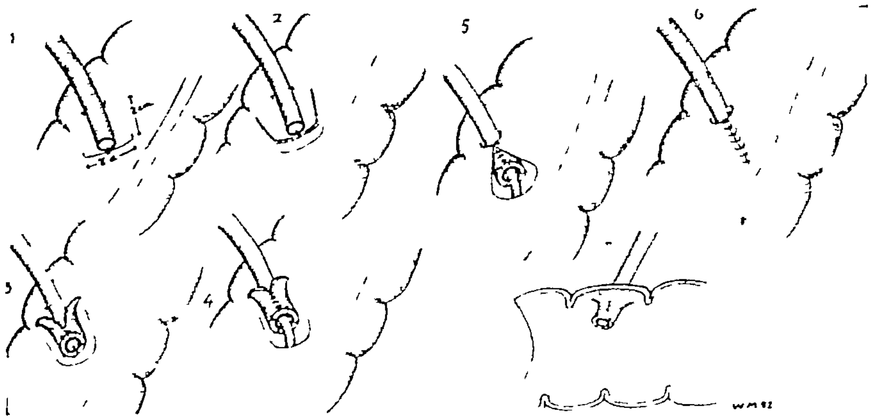

FIG 2A FIG 2B

FIG 2 New method for ureterointestinal anastomosis (Mathisen technique) *A*, preparing flap and closure around ureter *B*, closure of colon and view within colon (Courtesy of Mathisen, Willy Surg , Gynec & Obst , 96 255–258, 1953)

after recurrent pyelonephritis Ferris[13] noted that hyperchloremic acidosis occurred in 79 per cent of the 141 patients Bricker[14] stated that 30 per cent of 106 patients had pyelonephritis with ureteroileal anastomosis

Table 1 epitomizes the type of anastomosis utilized in various patients by the author The number of patients is tabulated along with those living after variable periods of time The resultant course of the majority of these patients is also shown, the chronological order of the method utilized ranges from above downward The various types of Coffey procedures were deleted because of the ills attending patients subjected to this method and observed elsewhere

Personal experiences and discussions with others had caused me to decide on a spatulate mucosa-to-mucosa ureterosigmoid anastomosis and diverting colostomy This virtually prevents the patient's having ascending pyelonephritis and attendant chemical imbalance

However, Mathisen[15] of Oslo, Norway has applied penetrating observation to adapt still another method of ureterointestinal anastomosis He had been dissatisfied with the direct or tunnel procedures because reflux up the ureter could often be demonstrated after the introduction of contrast media in the rectum He had observed that ureters in birds opened into the rectum on a small papilla similar to the common bile duct and thus were compressed by intracolonic pressure He devised a full thickness flap of the colon wall to surround the ureteral tip (fig 2) The ureter is cut straight across and fixed obliquely to the sigmoid with 0000 chromic catgut with atraumatic needle The colon is then incised along this margin with sufficient length to correspond with the circumference of the ureter It is then incised parallel to the ureter for a distance of 2 to 3 cm and the base is slightly broadened Interrupted sutures are then utilized to attach this bowel flap to the margin of the ureter and thus form a tube around it Continuous sutures are then extended up the flap to coapt its margins A tube is inserted in the ureter with its tip in the renal pelvis and the other tip withdrawn through the anus by means of tube or bougie Bleeding points are readily controlled by means of a fine needle electrode Bowel incision is then closed over the newly created nipple in transverse manner by two layers of suture Mathisen reported on 18 cases in 1953 stating that postoperative results had been encouraging and satisfactory in each

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The Mathisen method has been used for 7 patients from 1953 onward, it is regrettable that only one is now living C E was operated on in 1953 at which time cystectomy was performed because of infiltrating sessile type of vesical carcinoma Ureteral intubation was not resorted to Moderate ureteral and pelvic dilatation on the left side was present three weeks after operation (fig 3, *A*) He experienced pyelonephritis to a moderate degree on three occasions in the ensuing 6 months At that time excretory urography revealed mild dilatation of the right renal pelvis and he had experienced pyelonephritis once on this side (fig 3, *B*) One year after the operative procedure blood chemistry studies revealed blood urea nitrogen of 16 mg per cent and serum chlorides of 108 m/Eq, which continued until his demise Pyelograms were essentially unchanged but in the upright position, drainage seemed unimpeded (fig 3, C) The patient expired in October 1955 because of biliary cirrhosis I was unaware of his demise but was informed that the anastomotic site did present a good nipple with no encroachment on the ureteral lumina There was little evidence of pyelonephritis while the pigment precipitated within the tubules is bile (fig 4)

M H, aged 70, had a nonfunctioning right kidney due to 3 cm flattened invasive epithelioma of the bladder Ureteral intubation with short polyvinyl tubing was used at operation His recovery was quite good from the operative procedure until the tenth day at which time the Cherney curvilinear lower abdominal incision separated in its midportion Absorbable catgut sutures had been utilized throughout to reapproximate the fascial layers and wire sutures had not been used This was regrettable since this precept has been utilized in nearly all instances in which elongated incisions have been made The Cherney incision does not seem to afford any greater access to the bladder than the well retracted long midline incision Good right renal function was evident 3 months after cystectomy and anastomosis (fig 5) This patient had three bouts of cerebral embolism resulting in partial hemiplegia from which he made rather rapid recovery He acquired bronchial pneumonia which was fatal nine months after the operative procedure Preoperative nonprotein nitrogen was 50 mg per cent which rose to 80 three days after the operation and subsided to 35 within 3 months, it was 40 shortly before his demise

B K, aged 58, was only aware of urethral bleeding shortly before examination which revealed a nonfunctioning right kidney due to a 4 cm sized epithelioma of the bladder Her postoperative course was marred by the fact that an overly long 20 cm section of polyvinyl tubing was used for the left ureter The colon

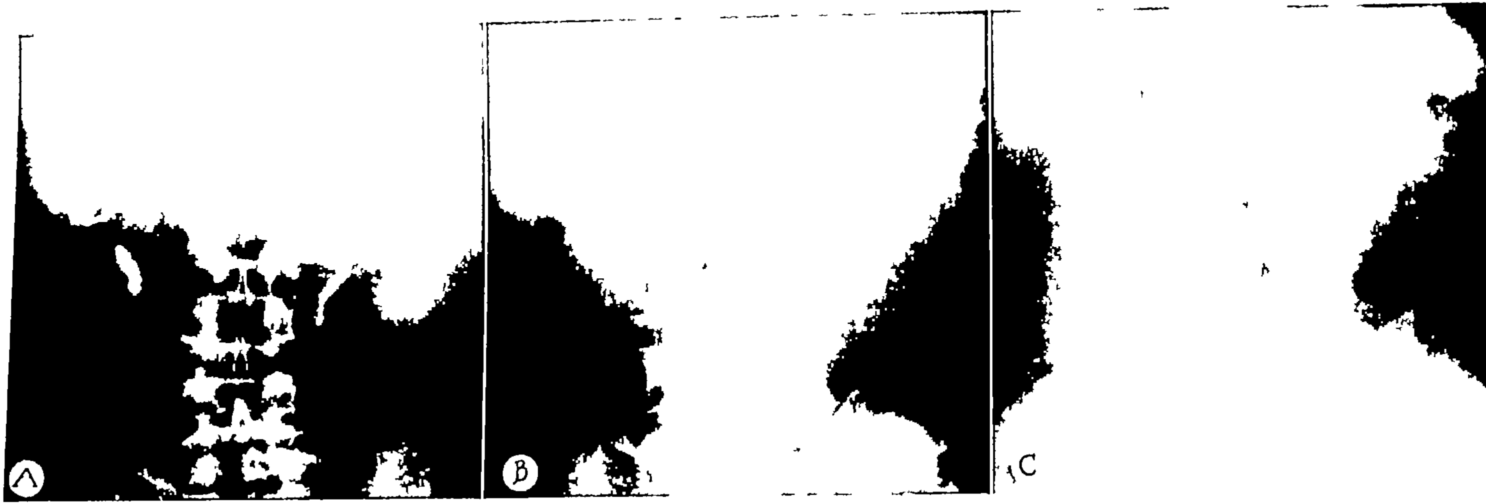

Fig 3 Mathisen anastomosis *A*, moderate dilatation of left renal pelvis and ureter, 6 weeks postoperatively Anastomosis was not intubated *B*, 6 months postoperatively Right pyelonephritis once *C*, unimpeded drainage in upright position

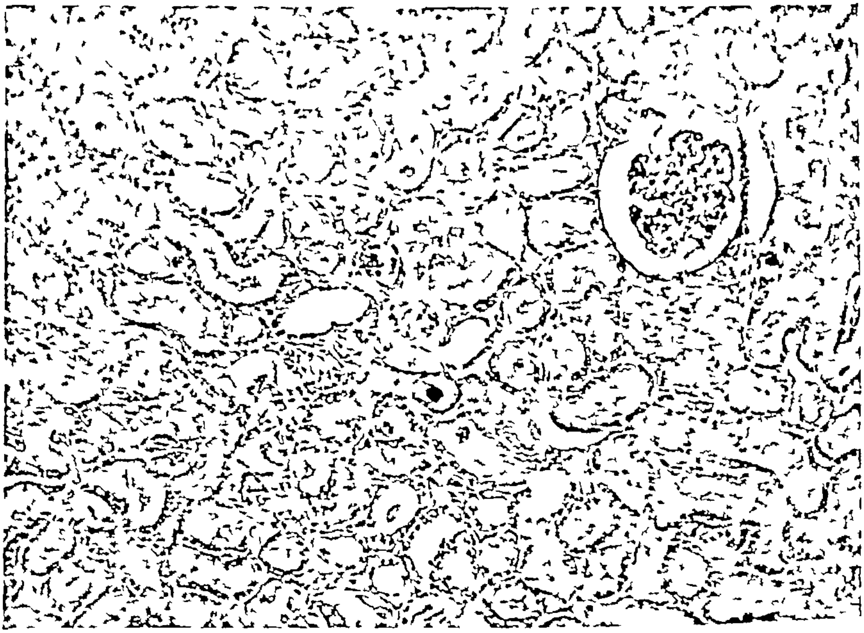

FIG 4 Patient died of biliary cirrhosis Little evidence of pyelonephritis Biliary pigment precipitated within tubules

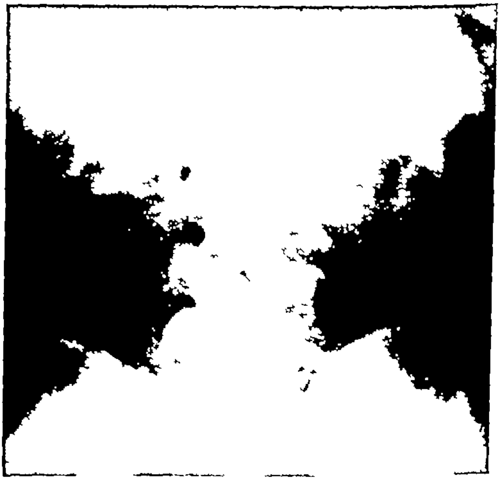

FIG 5 Three months after Mathisen anastomosis Nonfunctioning right kidney preoperatively Kidney is now functioning Left pyelogram is less distinct, but reveals good function

proximal to this area attached inferiorly to the iliac vessels of the pelvis and the splint tip coursed into this portion of the colon It was removed transcolonically 5 weeks after the first operative intervention Moderately soft calcareous material was seen in the inferior calyces at that time with moderate ureteral dilatation and pyelectasis This patient had bouts of pyelonephritis controlled by intermittent injections of 200 mg neomycin Vertebral metastases became evident 1

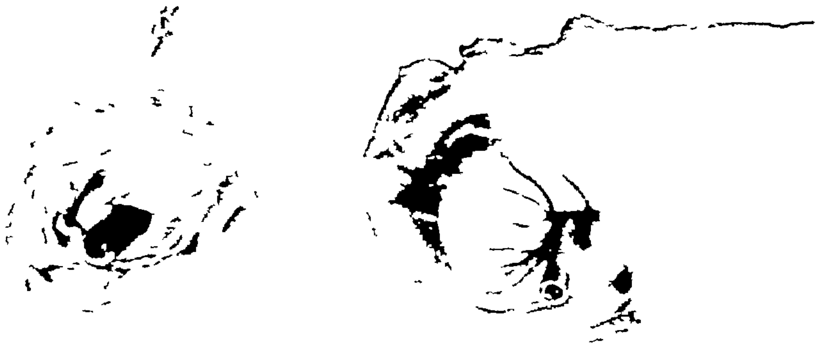

FIG 6 Mathisen anastomosis Nonconstriction of ureteral lumina These were photographed after formalin fixation Segment to left reveals papilla, segment to right shows left ureter retracted to one side

month before her rather sudden death apparently due to cerebral metastases Creatinine of 1 6 mg per cent was found on the day of her death Small segments of the removed colon and ureter appear in figure 6 The one to the left reveals rather a good papilla and represents the dilated right ureter while the right hand figure is from the left ureter revealing retraction of the lumen to one side This is the ureter which would not dislodge its long polyvinyl splint which was later removed transcolonically A moderate amount of mucoid purulent material was present in the left kidney while the right was moderately scarred and contracted from ureteral blockade which occurred preoperatively There was no calcareous material in the left renal pelvis

In spite of the fact that only one patient has survived more than 2 years, it seems to me, still, that this may afford an excellent procedure of combining both urinary and intestinal functions by way of the colon In the event of dilatation, pyelonephritic bouts or acidosis, a proximal colostomy would be indicated

DISCUSSION

Almost any patient can have ureterointestinal anastomosis and cystectomy performed as a single stage procedure The following patients, however, will require more sedulous evaluation and therapy those chronologically and physiologically over seventy, those with considerable impairment of the cardiovascular system those with advanced pulmonary fibrosis, those with impaired cerebration and those who will not accept or tolerate the necessary alterations to their mode of living

Peritonitis and ileus are seldom of consequence because of the excellent control of infection afforded by the insoluble sulfones and neomycin Intermittent nasogastric suction usually suffices but routine insertion is not a requisite Incisions in the posterior peritoneum over the ureter are utilized to fix the descending colon in transverse manner over the fifth lumbar area This peritoneum then covers the anastomosis and rotates the colon in such fashion that the ureter is not compromised by kinking or curving sharply Generous excision of the peritoneum over the bladder, rectum and extended laterally to the iliac vessels affords their exposure Areolar tissue and lymph channels are more readily removed along with the bladder, inferior ureters, supporting fascias, prostate and seminal vesicles This loss of peritoneum militates against its closure, in fact it need not and should not be closed since the space occupied by the bladder will collect blood and serum inviting localized infection Regeneration is rapid and there is little hazard of intestinal obstruction Perineal drains of fenestrated soft polyvinyl tubing afford excellent drainage The abdominal wound is reinforced by retention, interrupted, multistrand steel sutures over buttons

Artful application by the anesthesiologist has improved the lot of the patients subjected to long and extensive surgery Maintenance of blood volume gauged by the weighed blood loss or more accurately by means of radioactive iodinated albumin is a most prominent factor in improved postoperative recovery Intubation of the ureter is unnecessary in the direct mucosa-to-mucosa anastomosis but it should be utilized for either the tunneling or the Mathisen nipple procedures to prevent ureterectasis secondary to obstructive edema Long rubber or woven ureteral catheters may be inserted to the renal pelvis while the other end is attached to a colon tube manipulated and withdrawn through the anus The use of 10 or 12 cm lengths of beveled, soft, polyvinyl intravenous tubing provides an excellent splint Long heavy silk sutured to the emergent tip of tubing is appropriately knotted for right and left identification and is directed down the colon A stitch of fine chromic through the ureteral margin and tube retains the tubing in place for 7 to 10 days Free ends of silk emerge from the rectum in a few days and are extracted thereafter A four wing, sized 30 to 32 Malecot tube usually provides excellent rectal drainage Bulb syringe irrigation is performed three times daily and the tubing withdrawn whenever fecal obstruction has occurred

Neomycin (200 mg) is injected twice daily for the first week and then decreased for another week or two postoperatively Nonabsorbable sulfones are continued by oral route for another 3 weeks to aid in protecting the urinary system from infection

CONCLUSIONS

Refinements in the technique of ureterointestinal anastomosis have not prevented constriction or protected the kidney from ascending infection in all instances

Hyperchloremic acidosis occurs more often with anastomosis of the ureter to the colon when compared with those patients who have colostomy, ileal segments or cutaneous exit of the ureter

Acidosis is a reflection of renal function It is secondary to pyelonephritis

Patients with ureterointestinal anastomosis must be inspected periodically, since renal infection and impaired function may occur in a subtle manner in patients with seeming physiologic balance

Creation of a valve mechanism which does not impede the egress of urine or permit reflux from the intact colon has not been satisfactorily attained

Division of the colon provides a reservoir for urine in the rectosigmoid area This assures good renal function with little likelihood of infection or the prospect of acidosis Colostomy is acceptable to most patients

Mathisen "nipple" around the tip of the ureter within the colon assures good renal function in most instances Proximal colostomy may be performed subsequently if pyelonephritis, constriction, acidosis, or dilatation occurs

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THE ISOLATED ILEAL SEGMENT IN URINARY SURGERY

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During the past 60 years occasional cases have been reported in which surgeons utilized the ileum for reconstructive urinary surgery However, a satisfactory evaluation had to await the advent of antibiotics and present day supportive therapy One of the first successful ureterointestinal transplants performed experimentally was to a segment of isolated ileum Tizzoni and Foggi (1888) performed a two-stage operation on a dog, isolating an ileal segment in the first stage In the second stage they did a cystectomy and anastomosed the distal end of the ileum to the prostatic urethra after transplanting the ureters to the proximal end of the isolated segment of ileum The dog was described as alive and well two months postoperatively Numerous investigators in the early 1900's considered the small bowel unsuitable for urological surgery because of its primary function of absorption Their experimental animals met rapid death when the ureters were transplanted to the small bowel left in continuity rather than producing an isolated ileal segment

In the past few years various new uses for the ileum in urinary surgery have been described Doubtless more uses will be discovered At present isolated segments of ileum are being utilized in five ways 1) for urinary diversion to the skin, 2) as a substitute for all or a portion of a diseased ureter, 3) to propel urine where normal tonicity of the ureter is lost, 4) to increase bladder capacity 5) as a valve for urinary continence

The small bowel has been found satisfactory for urological surgery because of its rich blood supply and mobility It is possible to anastomose it to either renal pelvis or the bladder Its tubular structure and strong peristalsis are also of paramount importance A disadvantage frequently described in experimental animals has been formation of mucus plugs with urinary obstruction As yet this has not been a serious factor in the human Its major disadvantage has been its absorptive power However, in cases of urinary diversion utilizing the ileal segment, such as in the Bricker operation, electrolyte disturbances have usually been no problem Bricker (1952) reported 55 ureteral ileal anastomoses and cutaneous ileostomy with generally gratifying results Urine can safely be diverted to an isolated segment of exteriorized bowel without fear of electrolyte disturbances provided renal function can handle any minor absorptive problems These observations do not answer the question as to what may be expected when ileum is utilized for reconstructive urinary surgery keeping the urinary tract in continuity Very few experiments to answer this question have thus far been reported However, numerous clinical cases have now been described in the literature, and electrolyte disturbance has been no major problem Pyrah et al (1955) suggest

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that sodium and chloride are probably equally absorbed in contrast to selective chloride absorption in the sigmoid They also feel that potassium is absorbed With usual urinary potassium levels, hyperkalemia can be expected in the presence of impaired renal function Before discussing the specific cases, some mention should be made of preoperative management of the patient and surgical preparation of the isolated ileal segment

PREOPERATIVE PREPARATION

In cases of cystectomy where the final decision as to what is to be done with the ureters awaits surgical exploration, the bowel should be sterilized in the usual fashion, since it may be decided at surgery to utilize the large bowel rather than the small bowel The small bowel is a relatively clean structure, and the usual vigorous bowel preparation for large bowel surgery which not infrequently leads to colitis postoperatively is probably not necessary if it is known before surgery that a segment of small bowel is to be utilized Streptomycin orally for 2 days, or neomycin for 1 day preoperatively is satisfactory Cathartics and cleansing enemas make handling of the bowel simpler We consider the insertion of a Harris tube into the small bowel an absolute necessity This is done 36 hours preoperatively, thus allowing sufficient time for the tube to pass into the small bowel The night prior to surgery the tube is connected to suction to further decompress the small bowel for ease of handling at surgery Postoperatively, with this tube in place the fear of a blowout at the site of re-anastomosis is minimized In our experience the presence of the intestinal decompression tube has contributed immensely to the comfort of the patient postoperatively

When a surgical appliance such as the ileostomy bag is to be used, it is recommended that the appliance be acquired preoperatively and fitted to the patient in various positions to assure its proper placement on the abdomen with respect to the waistline since this is of utmost importance to the patient's comfort

PREPARATION OF THE ILEAL SEGMENT

The terminal ileum is used because of its great mobility The segment should be taken at least 6–8 inches proximal to the ileocecal valve taking care not to disturb the ileocolic artery which is the common blood supply to the distal ileum and cecum (fig 1, *A*) Before isolating the segment, the mesentery should be carefully examined preserving a maximum blood supply to the isolated segment of ileum In dividing the mesentery, the incision should go no deeper toward the base of the mesentery than is absolutely necessary to mobilize the segment as the chance of disturbing the blood supply is increased the nearer division is made to the base of the mesentery In our experience it is advisable early in the procedure to tag one end of the segment with a suture to be sure of the direction of peristalsis later in the procedure It seems reasonable to place the ileum in its new site so that propulsion of urine is in an isoperistaltic direction

After isolating the ileal segment, the continuity of the small bowel is restored by end-to-end or side to side anastomosis bringing the isolated segment out inferior to it (fig 1, *B*) Great care is exercised in closing the mesentery to avoid later herniation of bowel through it For the same reason, the transplanted seg-

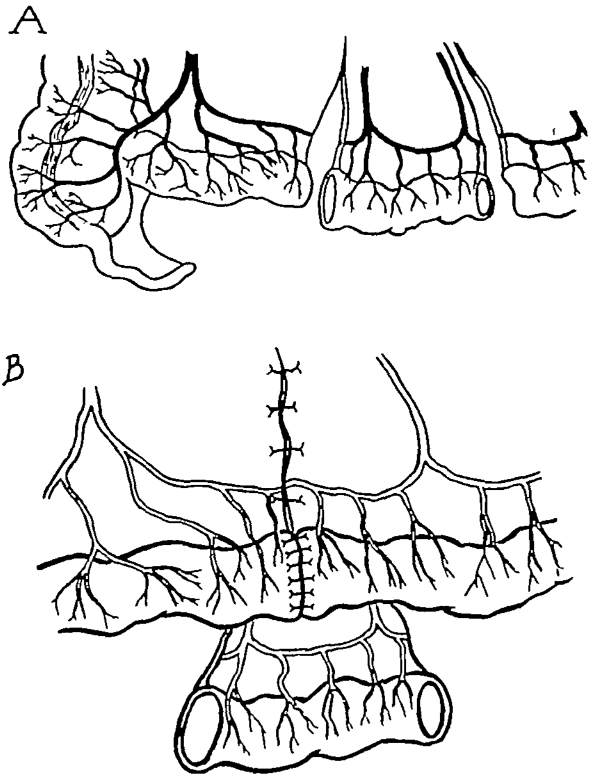

FIG 1 *A*, common blood supply to cecum and terminal ileum (ileocolic artery) *B*, prepared ileal segment with intestinal continuity restored

ment of ileum should later be secured to the peritoneum After preparing the segment, the procedure varies depending on what is planned Of prime importance is a good anastomosis between ureters and bowel with the avoidance of stricture formation A valve effect at this anastomosis is generally not so important, and for this reason we prefer a mucosa-to-mucosa anastomosis, generally in two layers utilizing fine catgut

The specific uses of the ileal segment can now be discussed in greater detail

THE ILEAL SEGMENT FOR URINARY DIVERSION TO THE SKIN

The operation of ureteroileostomy with cutaneous ileostomy was popularized by Bricker who used it for urinary diversion in cases of pelvic evisceration when it was necessary to remove the sigmoid In these cases the ileum acts as a conduit rather than a reservoir as is the case with the intact sigmoid In addition to its use in cases of radical surgery for carcinoma, the ileum has been successfully utilized as a means of diverting urine in children and in paraplegics with fecal and urinary incontinence We have not yet had experience with such a case and would imagine it is probably quite difficult to decide at what stage in the course of a disease process this procedure should be performed

Recently we found another use for the ileal segment as a means of diverting the urine

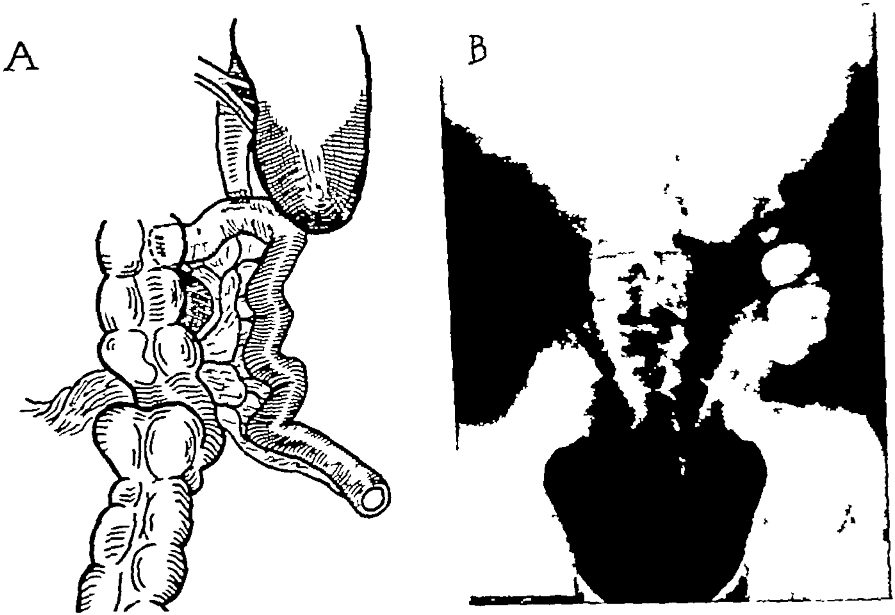

FIG 2 *A*, pyeloileostomy with cutaneous ileostomy *B* postoperative excretory urogram Retrograde filling of ileum demonstrates ileum in case of pyeloileostomy with cutaneous ileostomy

A 28-year-old man (H H No 15374) had pulmonary, bilateral renal, and bone tuberculosis since childhood Right nephrectomy had been performed at an early age because of advanced disease on that side and the presence of tuberculous cystitis Severe stricture later developed at the left ureterovesical junction necessitating a cutaneous transplant for drainage of the solitary left kidney This functioned satisfactorily for some time but eventually became obstructed making nephrostomy necessary This in turn functioned satisfactorily for about three years but became increasingly more difficult to handle and to catheterize The patient passed calculi through the sinus tract on one or two occasions After much consideration and consultation it was elected to perform a pyeloileostomy (fig 2, *A*) with removal of the renal calculi This was done on August 2, 1955 isolating a segment of terminal ileum and then bringing it with its mesentery through the mesentery of the descending colon thus placing the isolated segment in a retroperitoneal position The proximal end of the isolated segment was easily mobilized to the pelvis of the left kidney The distal end of the ileum was brought out on the left lower abdomen well away from the umbilicus and anterior-superior spine of the ilium to insure satisfactory fitting of an ileostomy bag

The patient is able to handle the bag by himself and finds its position much more satisfactory than a flank nephrostomy tube He reports with pleasure that for the first time in many years he has been able to appear on the beach in a bathing suit It is planned to attempt to increase the bladder capacity and restore urinary continuity at a later date Thus far the blood urea nitrogen has remained normal with slight increase in plasma chlorides Figure 2 *B* is a postoperative excretory urogram It was interesting to note that at the time of these pyelograms the ileum could not be demonstrated For the sake of a definitive radiograph it was necessary to instill radiopaque material in a retrograde fashion by means of gravity This has been noted by others and suggests that active peristalsis in the ileum probably tends to diminish reflux of urine into the kidney

Bricker reviewed the complications of ureteroileostomy as a means of urinary diversion in 55 transplants There were 2 deaths directly attributed to the technique of ureterointestinal anastomosis and preparation of the ileal segment Two additional cases expired following convulsions, the cause of which remained unexplained even after autopsy Experimental studies by Tasker (1953) would suggest that hyperkalemia might have been the explanation for death in these 2 cases Early postoperative complications also included 3 cases of intestinal obstruction relieved by nonoperative measures A perineal urinary fistula and transient anuria developed in one case Cultures from ileal segments were rarely sterile and chiefly revealed coliform bacteria

A personal case in which the author utilized the Bricker operation for palliation in a case of bladder cancer is included in this discussion because of the very good results observed pyelographically The patient's clinical course was not altered considerably by this procedure However, following the Bricker operation he was not disturbed by urinary frequency, hematuria, or bladder pain

A 69-year-old man (H H No 106341) had a transurethral electroresection of the prostate for benign hyperplasia several months previously At that time a small lesion was noted in the bladder and resected It was reported as transitional cell carcinoma invading the muscularis It was elected not to perform cystectomy (in retrospect, a wrong decision), and the patient failed to return for followup examinations Several months later he appeared with severe hematuria of several days' duration requiring blood transfusions and transurethral resection to control bleeding from a large recurrent bladder tumor extending into the prostatic urethra Bimanual examination disclosed a fixed, palpable mass The blood urea nitrogen was normal, but excretory urograms showed severe hydronephrosis on the right due to ureterovesical obstruction and no function of the left after several hours An antegrade pyelogram (Casey and Goodwin) on the left side demonstrated severe hydronephrosis also due to ureterovesical obstruction (fig 3, *A* and *B*) Roentgenographic studies of the bones disclosed a metastasis in the left femur at its distal end A Bricker operation was performed for palliation on July 7, 1955 leaving the bladder in situ Postoperative pyelograms demonstrated prompt bilateral renal function with much improvement in the appearance of the left hydronephrotic kidney (fig 3 *C*) The patient expired two months later from inanition and cancer At the time of his death the bone metastasis had grown in size to be palpably apparent, and the bladder tumor extended into the shaft of the penis Throughout his postoperative course and to the time of his death the blood urea nitrogen remained normal with no electrolyte disturbance and no episode of pyelonephritis He was relieved of bladder discomfort

THE ILEUM USED AS A SUBSTITUTE FOR THE URETER

There have been about 25 cases of this nature reported In these a segment of ileum has usually been utilized to replace a long strictured area in the lower third of the ureter after extensive pelvic surgery for carcinoma These cases are not

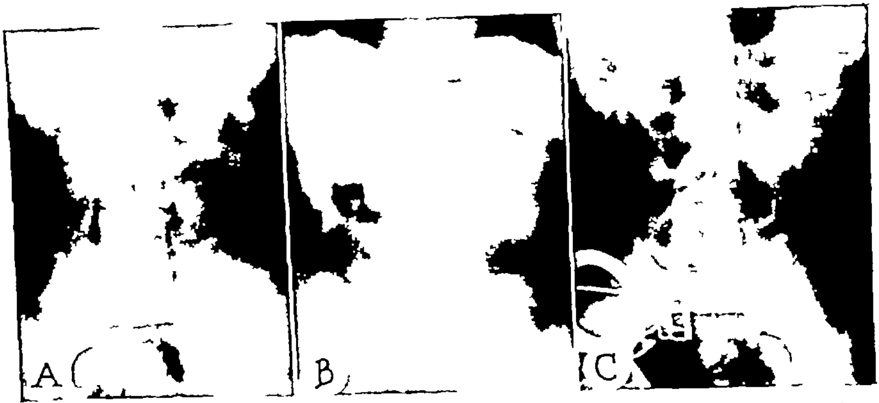

FIG 3 *A*, 3 hour delayed preoperative excretory urogram in case of severe bilateral hydronephrosis secondary to incurable bladder tumor showing no function on left *B* left antegrade pyelogram on same patient *C*, postoperative excretory urogram of same patient with prompt function bilaterally

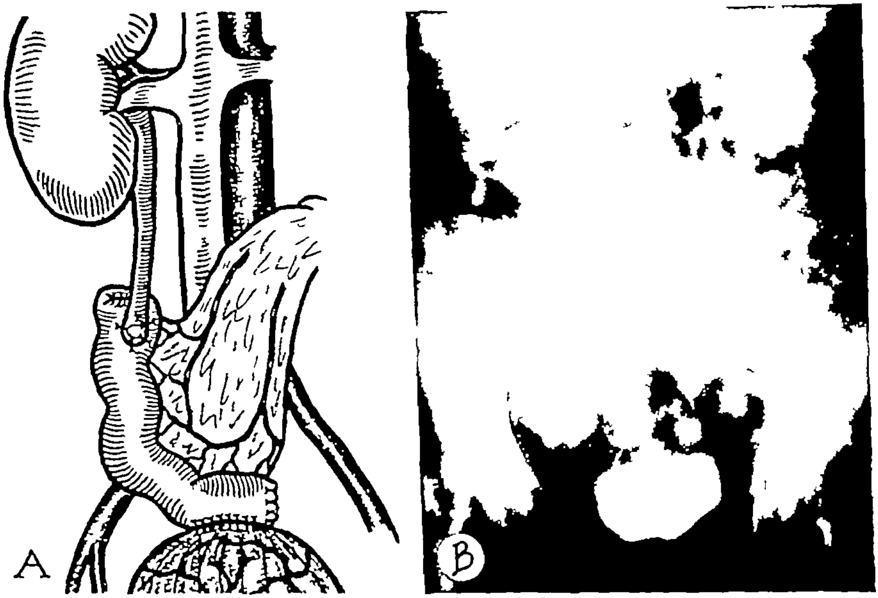

FIG 4 *A*, method of repair used to remedy strictured right ureter *B*, postoperative pyelogram on same patient

amenable to repair of the ureter by means of a bladder flap We have followed such a case for two years since substitution of a segment of ileum for the right lower ureter The patient had a Wertheim operation and later a ureterovaginal fistula and destruction of the lower third of the right ureter developed Figure 4, *A* shows the method of right ileal substitution and figure 4, *B* represents an early postoperative pyelogram demonstrating the ileal segment and its relation to the bladder A recent excretory urogram disclosed prompt function with minimal hydronephrosis The patient has done well, with no electrolyte disturbances She has some incontinence of urine when in bed at night but does not

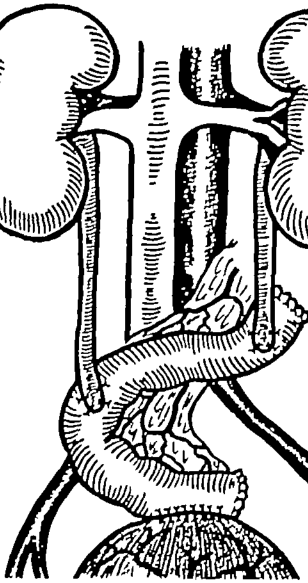

Fig 5

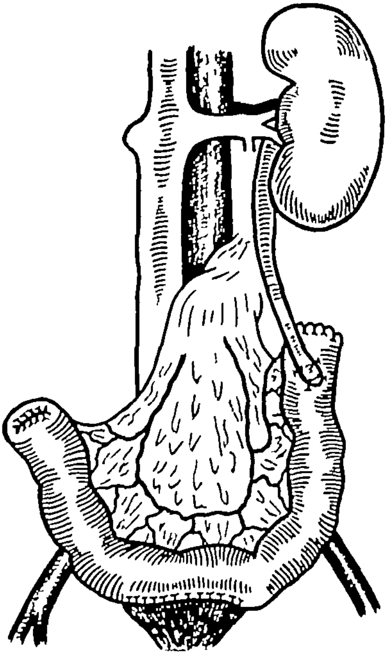

Fig 6

Fig 5 Bilateral ureteroileostomy for strictured ureters
Fig 6 Ileocystoplasty

leak urine during the day This procedure has also been carried out for bilateral ureteral strictures (fig 5) by Moore et al (1956) with good early results In addition to this use in patients with lower ureteral strictures, it has been employed by Baum with success for a stricture at the ureteropelvic juncture in a solitary kidney which remained unimproved after three conventional plastic procedures

Pyrah has utilized a segment of ileum to replace a portion of ureter removed because of primary ureteral papilloma or carcinoma If one is certain that such lesions are primary in the ureter rather than implants from the kidney, there is no contraindication to handling such a tumor in this manner

THE ILEAL SEGMENT TO PROPEL URINE WHEN NORMAL TONICITY OF THE URETER IS ABSENT

For completeness this is included in uses of the ileal segment, although no truly satisfactory investigation has been carried out as yet It seems reasonable that in congenital atonic ureters some good might come from replacing the ureter with a tubular structure like the ileum which possesses strong peristalsis Baum attempted such a procedure on an 8-year-old girl who had bilateral ureterovesical stenosis with bilateral hydronephrosis and hydroureter She earlier had reimplantation of the left ureter with repeated urinary tract infections postoperatively due to reflux The left ureter was replaced by ileum and within one year postoperatively she had three episodes of urinary tract infection Pyelograms remained unchanged The urine gradually cleared of mucus and contained only 5–6 white blood cells Cultures were never sterile While one such case cannot allow us to draw definite conclusions, such information should be retained for possible use in any severe situation where other treatment has failed *

THE ILEUM TO INCREASE BLADDER CAPACITY

Couvelaire (1950) and Cibert (1954) have contributed to knowledge of this subject in carrying out their work on the contracted, inactive tuberculous bladder Cibert reports 23 cases of ileocystoplasty with relief of urinary frequency and return of continence In many instances there was appreciable improvement in the solitary hydronephrotic kidney Ferris (1955) reports good results following ileocystoplasty in a case of contracted bladder secondary to interstitial cystitis no longer responding to conventional treatment Figure 6 illustrates one method of ileocystoplasty

THE ILEUM AS A VALVE FOR CONTINENCE

Smith and Hinman (1955), dissatisfied with the usual management of children with urinary leakage secondary to neurological disorders, conducted a series of experiments in the dog anastomosing the ileal segment to the bladder in an antiperistaltic fashion, bringing the proximal end out on the abdomen They found, after closing the vesical neck, that if sufficient length of ileum was used, the dogs were continent By producing an intussusception in the ileal segment, they believed that the bladder would remain full until catheterized or until it became overdistended With that knowledge they have recommended using the procedure on children with the idea of closing the bladder neck and catheterizing the bladder when full, thus avoiding an indwelling catheter A final report from these workers will be of interest Regardless of outcome, knowledge gained from these experiments is of permanent value With this information other uses for the ileum in urinary tract surgery might be conceived For example, in case of extensive trauma to the urethra and sphincter beyond reconstructive plastic repair, a "urethra" could be constructed in an antiperistaltic manner from the ileum and brought out on the lower abdomen or perineum through a skin flap which would act as a urinary conduit with hope of achieving continence if the length of ileum is adequate

SUMMARY

The advantages and disadvantages of the isolated ileal segment, as well as its various uses in urinary tract surgery, have been discussed Three personal cases exemplifying these uses are presented One is a case using the ileum as a means of urinary diversion (Bricker operation) Another represents use of ileum to achieve satisfactory pyelocutaneous urinary diversion in a patient with a solitary kidney and severe tuberculosis A third is a case in which the ileal ureter was employed following damage from extensive pelvic surgery

CONCLUSIONS

The isolated ileal segment is a satisfactory structure for use in reconstructive urinary tract surgery Further clinical use of this valuable structure in cases

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* Swenson recently reported the successful use of the ileal segment in several cases of megaloureter

similar to those discussed is justified Other new uses for the ileum in urology may yet be developed

The author wishes to express appreciation to Dr Willard Goodwin and Dr Elmer Belt of the Department of Urology and to Dr Beryl Averbook of the Department of Surgery for their guidance, advice and encouragement Photographs by Mr William Martinsen and the photographic laboratory at Wadsworth Hospital made possible a graphic presentation of the work

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SERUM PROTEIN ALTERATIONS IN UREMIA I ELEVATED ALPHA-2 GLOBULIN IN DOGS*

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Bilateral ureteral ligation[1] and various modifications[2] have long been used as a method for inducing uremia rapidly in experimental animals Although some serum constituents such as creatinine, guanidine and phenol have been excluded as causative of uremia,[3-5] no substance or group of agents has been identified as etiological

It is reasonable to assume that the "toxin" of uremia, whether produced in the kidney or elsewhere, would appear in plasma as a non-dialyzable[6] protein-like factor[7, 8] Therefore, a survey of serum proteins by filter paper electrophoresis[9] should disclose any significant qualitative changes in serum protein configuration Results of such an analysis, performed on sera of dogs made acutely uremic by ureteral ligation and sustained for several days in this state by use of ion exchange resins,[10] are herein reported

MATERIALS AND METHODS

Mongrel dogs of both sexes, of varying ages, and about 12 to 25 kilograms in weight, were subjected to bilateral distal ureteral ligation and section through a midline intraperitoneal incision under intravenous "veterinary nembutal" (Abbott) anesthesia, in dosage of 5 mg per kg body weight

In one group (group 1), consisting of 15 animals, no therapy was given postoperatively The usual survival period in this group was 72 (±10) hours (table 1) Although intermediate data were similar in every instance, seven of these dogs were excluded from the study because they died unobserved during the night The remaining 8 dogs which were acceptable for the study were sacrificed when

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* The initial portion of these studies was performed at the Francis Delafield Hospital, Columbia Presbyterian Medical Center, New York, N Y

This work was partially supported by the contribution of Mr Daniel E Koshland, San Francisco

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similar to those discussed is justified Other new uses for the ileum in urology may yet be developed

The author wishes to express appreciation to Dr Willard Goodwin and Dr Elmer Belt of the Department of Urology and to Dr Beryl Averbook of the Department of Surgery for their guidance, advice and encouragement Photographs by Mr William Martinsen and the photographic laboratory at Wadsworth Hospital made possible a graphic presentation of the work

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TABLE 2. *Marked elevation of serum alpha 2 globulin in prolonged uremia*

Dog No.	Alpha 2 Globulin Hours after Ureteral Ligation					
	24	48	72	96	120	150
U-R-1	E	E	E	E		
U-R-2	E	E	E+	E+		
U-R-3	N	E	E+	E+	E+	E+
U-R-4	N	N	E	(Killed at 80 hours—Possible distemper)		
U-R-5	E	E	E+	E+	E+	
U-R-6	E	E+	E+	E+		
U-R-7	E	E	E+	E+	E+	
U-R-8	N	E	E	E+	E+	
U-R-9	E	E	E	E	E+	E+

N = "Normal", E = "Elevated", E+ = "Greatly elevated"

once daily thereafter 15 gm. sodium salt carboxylic acid type ion exchange resin was administered in 2 minutes by bulb syringe through a stomach tube. At the same time, similarly mixed in about 50–75 cc. water, 15 gm. hydrogen cycle carboxylic acid type resin was rapidly instilled by rectal tube each day.

Initially, electrocardiographic recordings were made daily, as were determinations of blood urea nitrogen, sodium, potassium, chlorides and bicarbonate. Since these values assumed uniform patterns at the several different study periods throughout progressing uremia, they were discontinued. These ancillary data are not reported here, inasmuch as they demonstrated only well-known acidotic, hyperkalemic alterations.[14]

In initial determinations the apparatus and technique described by Osserman and Lawlor[15] were used.* The patterns first recorded were duplicated in all subsequent studies. (The latter were performed with the Model No. 1404 electrophoresis apparatus manufactured by the Research Specialties Co., Berkeley, Calif.) Four serum specimens, each of 2-lambda volume, were applied to the same Whatman No. 1 filter paper strip for a typical electrophoretic migration. The filter paper strip was washed in buffer solution, blotted free of excess buffer and allowed to equilibrate at 500 volts with 3–4 milliamperes current for about 30 minutes prior to application of the serum samples. Best resolution of serum protein components was achieved by maintaining a constant 500-volt, variable 3–5 milliampere current for 5–6 hours, using a 0.09 M veronal buffer, pH 8.6 in 12 per cent propylene glycol at room temperature.† (The latter agent served to minimize distillation from the filter paper.) Bromphenol blue was applied to the

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* Sincere thanks are due Miss Lawlor for the electrophoretic determinations performed in New York, in the preliminary portions of this study.

† Optimal conditions of the electrophoresis were arrived at by varying buffer concentration (0.05–0.1 M), duration of migration (4–12 hours), current (2–10 mA), and voltage (100–500 V).

TABLE 1 *Status of serum alpha 2 globulin following ureteral ligation*

Dog No	Alpha 2 Globulin Hours after Operation									
	8	16	24	32	40	48	56	64	72	Over 72
U-1	N	?E	E	E	All Elevated					
U-2	L	N	N	E						
U 3	N	N	E	E						
U-4	N	?E	?E	E						
U 5	N	N	N	?E						
U 6	?L	E	E	E						
U 7	N	N	E	E						
U-8	N	E	E	E						

N = "Normal", L = "Low", E = "Elevated"

considered terminal (or unlikely to survive throughout the night) by thoracotomy performed under small doses of intravenous nembutal The chest was opened in order to excise the beating heart for study of myocardial cholinesterase, as reported elsewhere [11]

In group 2, 9 animals were sacrificed and considered acceptable according to the considerations indicated for the preceding aggregation In the present group the animals were maintained postoperatively by oral and rectal administration of ion exchange resins,* [12] and by parenteral fluid administration, as will be noted in detail later As indicated in table 2, these animals survived 96 to 150 hours

The control group (group 3) consisted of 10 dogs, apparently in good health grossly, which were untreated either by operation or supportive measures

Serum specimens were drawn from leg veins on 2 separate occasions in the control animals and preoperatively in all others Following ureteral ligation, serum specimens were taken every 8 hours After clotting, the serum was aspirated, stored in sterile containers at 4°C and subjected to electrophoresis within 8 hours to 30 days † In addition, just prior to sacrificial thoracotomy, the blood was collected from a carotid artery and similarly stored This blood was subsequently subjected to sodium sulfate precipitation for separation of alpha-2 globulin in quantity [13]

All animals in group 2 were given from 200 to 400 cc fluid by hypodermoclysis once daily, starting with 5 per cent dextrose in 0 9 per cent saline solution at 12 hours after ureteral ligation, and 5 per cent dextrose in water each day thereafter until sacrificed No oral intake was allowed, but 24 hours after operation and

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* The ion exchange resins were generously provided by Dr E L Martz, Eli Lilly and Co , Indianapolis, Indiana

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† No difference in electrophoretic migration was observed within 30 days Random determinations remained unchanged up to 3 months

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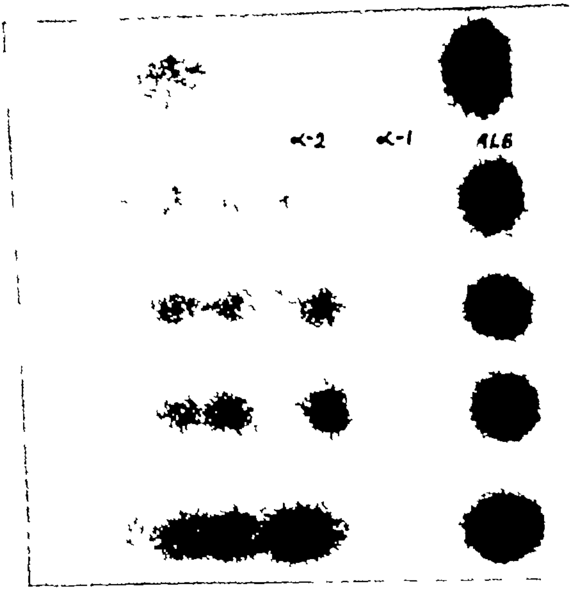


FIG 1 Gradual increase in serum alpha 2 globulin (dog U R 2) Stain intensity increased during each day of increased survival in uremia Parenteral fluids plus oral and rectal ion exchange resins instituted commencing 24 hours after bilateral ureteral ligation

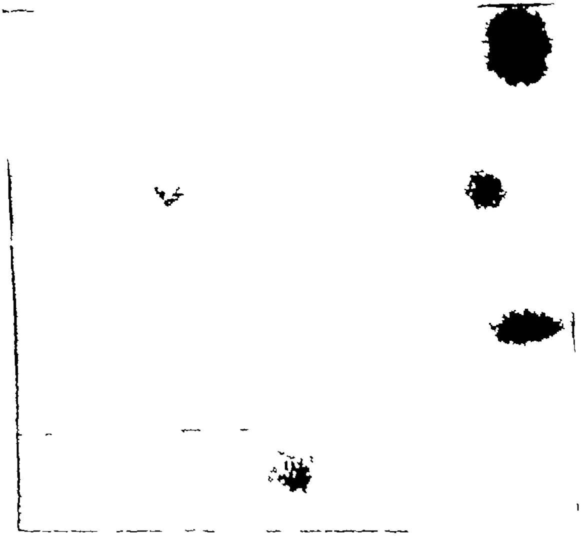


FIG 2 Comparisons of normal and uremic serum alpha 2 globulin Uppermost electrophoretic migration represents a typical pattern from an untreated "control" animal of group 3

Middle line depicts elevation of alpha 2 portion of serum protein of dog U-7 (group 2) at 72 hours after ureteral ligation No subsequent treatment Sacrificed at 80 hours, since overnight survival unlikely

Bottom pattern illustrates depth of stain intensity of alpha 2 globulin area taken from animal kept alive by parenteral fluids and ion exchange resins to 150 hours following bilateral ureteral ligation (dog U R 9, group 2)

Supplementary line indicates good separation of alpha 2 globulin by differential sodium sulfate precipitation Slight residuum of albumin is seen in this instance, but better elimination of this fraction is usual serum specimen prior to electrophoresis in order to visualize the migration of protein (viz, the dye preceded the albumin) Following electrophoresis, the filter paper strip was blotted and dried at 80°C, then stained while still warm in a saturated solution of Buffalo Black (National Aniline Div, New York City) in 40 per cent ethanol—10 per cent acetic acid for 10 minutes The filter paper strip was then washed repeatedly in the ethanol-acetic acid mixture to remove excess dye and, finally, blotted dry

Lastly, in order to verify the elevated fraction of serum protein in these uremic dogs as alpha-2 globulin, differential salting-out was performed according to the sodium sulfate method of Milne[13] Filter paper electrophoresis substantiated the identity of the alpha-2 globulin thus salted out from interval serum specimens during uremia and also from aliquots of serum drawn during the sacrificial exsanguination of each experimental animal

RESULTS

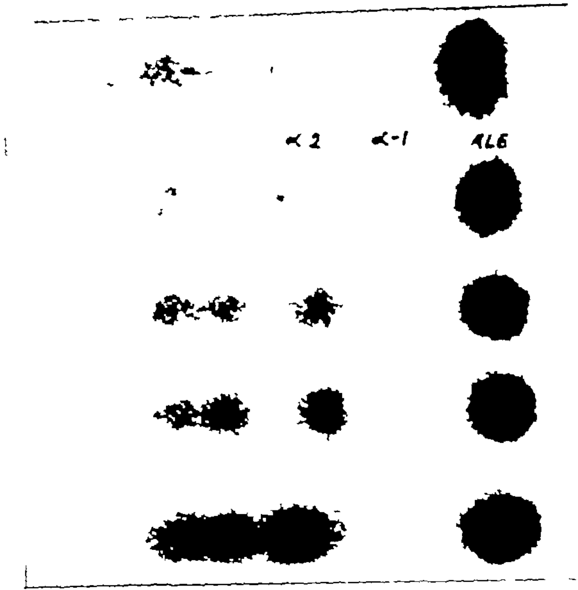
The 8 animals of group 1 appeared moribund within 48 to 90 hours following ureteral ligation Sacrificial exsanguination-thoracotomy was usually performed within 60–80 hours As indicated in table 1, there was elevation of alpha 2 globulin in the exsanguinating serum and in interval specimens starting at about 24 hours after ureteral ligation in most cases and in all instances within 32 hours

Although no classification was devised for the qualitative enhancements of serum alpha-2 globulin with longer periods of survival in the uremic state, such a tendency was suggested by gross visual scanning and comparisons of the electrophoretic patterns No quantitative measurements of electrophoretic results were done

Figure 1 illustrates progressive elevation of serum alpha-2 globulin each day following ureteral ligation and administration of ion exchange resins (dog U-R-2) Figure 2 demonstrates normal, "medium survival" and "prolonged survival" patterns of protein migration by filter paper electrophoresis of uremic sera These are compared with the "salted out" alpha-2 globulin derived from differential sodium sulfate precipitation

In table 2, levels of serum alpha-2 globulin are recorded for those animals in which uremic survival was prolonged by administration of fluids and of ion exchange resins after ureteral ligation Again, serum alpha-2 globulin is seen consistently to be elevated Preliminary studies by differential sodium sulfate precipitation of the alpha-2 globulin fraction indicate that quantitative increase develops as life in uremia is prolonged

The tables reveal that changes in uremic serum alpha-2 globulin were usually and clearly demonstrable by the electrophoretic and staining technique employed in this study 24 hours after ureteral ligation At the other extreme, the critical period for demonstration of marked concentration of alpha-2 globulin seemed to be 72 hours after ureteral ligation Although not shown in table 1, several animals in group 1 not treated with parenteral fluids or ion exchange resins manifested a sharp rise in the alpha-2 globulin beyond 72 hours Therefore,



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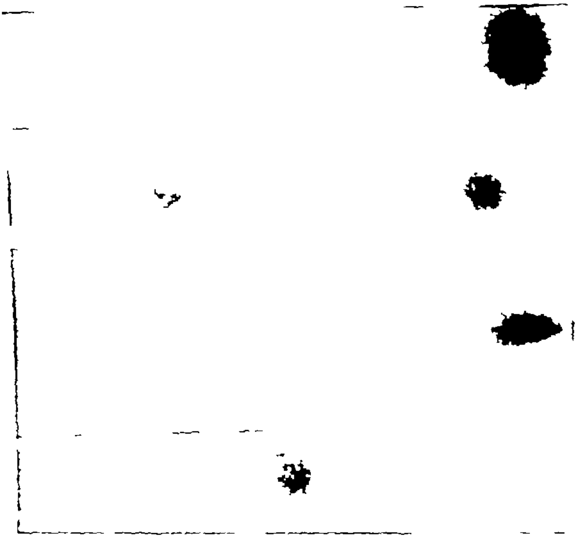

FIG 2 Comparisons of normal and uremic serum alpha-2 globulin. Uppermost electrophoretic migration represents a typical pattern from an untreated "control" animal of group 3

Middle line depicts elevation of alpha-2 portion of serum protein of dog U-7 (group 2) at 72 hours after ureteral ligation *No subsequent treatment Sacrificed at 80 hours, since overnight survival unlikely*

Bottom pattern illustrates depth of stain intensity of alpha 2 globulin area taken from animal kept alive by parenteral fluids and ion exchange resins to 150 hours following bilateral ureteral ligation (dog U-R 9 group 2)

Supplementary line indicates good separation of alpha 2 globulin by differential sodium sulfate precipitation Slight residuum of albumin is seen in this instance, but better elimination of this fraction is usual this elevation did not occur only in those dogs receiving supportive treatment after ureteral ligation

DISCUSSION

The significance of the rise in serum alpha-2 globulin in acute canine uremia, as demonstrated in the present studies, is equivocal and subject to various interpretations Firstly, it can not be stated whether the critical metabolic alterations which cause uremia[7] [16] or develop during uremia are reflected in the serum proteins or in their electrophoretic migrations Secondly, it is not known whether the "uremic toxin" is produced normally in the kidney, or only in the damaged kidney Also to be considered is the concept that the kidney may be injured in its futile attempts to excrete a protein-like material produced elsewhere in the body Thirdly, change in serum alpha-2 globulin is not unique to uremia and such alteration may be irrelevant Finally, as a general point, demonstration of a qualitative change in serum protein is inconclusive *per se* and falls short of identifying other types of measurable and unmeasured serum components

Since the fundamental chemical changes in uremia are unknown, the present report was intended only as a preliminary survey In that vein, qualitative electrophoresis was applied Quantitative separation of the alpha-2 globulin and its sub-fractions[17] [18] may be contemplated and the physiological effects studied in experimental animals

Houck[19] has been able to keep bilaterally nephrectomized dogs alive and active for several months In view of this startling result and the known uremic influence of renal damage in chronic glomerulonephritis,[20] it may be debated whether the kidney plays a direct or key part in the etiology of uremia On the one hand, *pre*-renal azotemia causes elevation in serum non-protein nitrogen, a basic criterion in defining "uremia " On the other hand, the kidney may produce an enzyme, while "uremia" develops, which acts upon some circulating substrate, or *vice versa* [7] As another possibility, products of deranged metabolism or debris from tissue damage anywhere in the body may produce anatomical and physiological injury to the kidney as the latter organ encounters these substances in its excretory role [21]

Review of the literature reveals that alteration of serum alpha-2 globulin has been found electrophoretically mainly in nephrosis[18] and infrequently in various cardiac and pulmonary diseases [17] Abnormal serum[22] and urinary[15] proteins have been found in multiple myeloma, to mention but one condition In consideration of the characteristic integrity of the plasma, as well as its variable constituency in the role of transporting vehicle,[23] the protein alterations must be studied discriminatingly Thus, the finding of elevated alpha-2 globulin in acutely induced uremia in dogs can not be construed as pathognomonic of acute uremia, or unique to the uremic state in general

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No extrapolation of experimental findings in animals can be proposed for the human subject Nonetheless, experimentally induced canine uremia and that encountered clinically have many features in common Therefore, a survey in progressive and in reversible human uremia, stemming from diverse mechanisms, appears justified and is being conducted [24] Assessment of *rate of change* of this globulin fraction in correlation with renal biopsies and clinically observed fluctuations of a given patient's uremia is planned in search for a rapid, accurate indicator of "depth of uremia "

SUMMARY

Qualitative elevation of serum alpha-2 globulin was observed by filter paper electrophoresis in acute canine uremia produced by bilateral ureteral ligation Increase in this protein fraction occurred in 5 of 8 dogs within 24 hours and in all within 32 hours In 9 dogs kept alive in uremia up to 6 days by parenterally administered fluid along with ion exchange resins given orally and rectally, marked elevation of serum alpha-2 globulin began at about 72 hours and progressed until death

Several interpretations for this finding are suggested It is apparently nonspecific Types of renal mediation in biochemical mechanisms theoretically fundamental to uremia are mentioned

Grateful acknowledgment is proffered to Dr Alfred Gilman, Department of Pharmacology, Columbia University College of Physicians and Surgeons, New York City, for his counsel in the initiation of this investigation

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TRANSURETHRAL RESECTION OF THE BLADDER NECK IN THE FEMALE

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Transurethral resection of the bladder neck in female patients is a surgical procedure which is infrequently performed It is however occasionally indicated, but many urologists are hesitant to do the operation The indications for its performance may not always be clear, the technique is not well standardized, the anticipated results may be unpredictable or poor, and the training and experience of the urologist may be inadequate to perform the operation properly

REVIEW OF LITERATURE

There are many lesions which may prevent the free expulsion of urine from the bladder in the female Table 1 is a classification of these lesions and includes references to pertinent literature Some of them are best treated by transurethral resection of the vesical orifice

The first recorded transurethral resection of the bladder neck in the female, as far as we have been able to find, was done by John Caulk in 1921 He obtained an excellent result Since then many cases have been reported (table 2)

The pathology of obstruction of the female vesical neck was first described by Ambrose Paré in 1575, then again by DeGroof in 1672 It was not until 1853 that Virchow concluded that the prostatic homologue in the female existed, based upon his observation of urethral glands and retained concretions in elderly women Tourneau presented his hypothesis in 1889 Von Brunn in 1883 described the vesical neck glands and glandular nests Glandular elements both urethrally and subtrigonally were also described by Albarran in 1909 Considerable controversy has existed in the past as to the existence of glandular hyperplasia or "female prostate" types of obstruction in the posterior urethra Excellent articles supporting this opinion are by Renner, Folsom, Young, Huffman, Johnson, Beneventi, Powell, Caldwell, Caulk, and Hyams Their findings have not been supported by Cabot, MacKenzie, or Thompson Histopathology of the present series includes and confirms the findings of these types and combinations of obstructive lesions

INDICATIONS FOR TRANSURETHRAL RESECTION OF THE BLADDER NECK IN THE FEMALE

One of the most common syndromes the urologist is called upon to treat in the female patient is frequency, urgency, burning on urination and pain in the urethra or bladder neck It is not always easy to determine the cause of these

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Read at annual meeting of Western Section of American Urological Association, San Francisco, Calif April 30–May 3, 1956

TABLE 1 *Classification of obstructions of the female vesical neck*

- I Congenital
  - A Contracture
  - B Stricture
  - C Valves
  - D Ureteroceles and polypoid mucosa
  - E Prolapse of redundant mucosa
  - F Muscular hypertrophy
  - G Periurethral glandular hyperplasia
    - 1 Mucosal enfolds
    - 2 Subtrigonal glands of Albarran
    - 3 Folsom's "female prostate"
    - 4 Brunn's glands
  - H Mucosal inclusion cysts
  - I Neurogenic
- II Acquired
  - A Inflammation
    - 1 Spasm
    - 2 Strictures or stenosis
    - 3 Periurethritis with abscess
    - 4 Fibromuscular hyperplasia
    - 5 Granulation tissue
    - 6 Round cell infiltration (lymphoid)
    - 7 Amyloid
  - B Trauma
  - C Mechanical
    - 1 Extrinsic
      - a Adjacent neoplasia
      - b Foreign body
      - c Cystocele
    - 2 Intrinsic
      - a Calculi
      - b Foreign body
      - c Urethral diverticulum with or without calculi
  - D Post-irradiation
  - E Neoplastic
    - 1 Benign
      - a Metaplasia
      - b Leukoplakia
      - c Polyps
      - d Endometrioma
      - e Papilloma
      - f Caruncle
    - 2 Malignant
      - a Transitional cell carcinoma
      - b Squamous cell carcinoma
      - c Adenocarcinoma
  - F Neurogenic
    - 1 Central nervous system
    - 2 Peripheral nerve lesions
  - G Glandular
    - 1 Virilizing tumors—Cushing's disease

TABLE 2 *Reported transurethral resections of the bladder neck in the female*

		No Cases Reported
1921	Caulk (first transurethral resections of bladder neck)	1
1933	Nesbit	3
1934	Hicks	3
1934	Fite	1
1935	Thompson	1
1935	Van Houten	6
1935	Caulk	12
1936	Winsbury White	2
1937	Caulk	15
1939	Thompson	24
1940	Loeb	1
1940	Baurys	5
1940	Young	3
1942	Thompson	31
1943	Mirabile	1
1943	Folsom, O'Brien	7
1944	Engels	4
1945	Coutts, Vargas	3
1946	Melville	1
1946	Jacobson	3
1948	Ritter, Shifrin	1
1948	Dees	6
1948	Shumacher, Henderson	15
1948	Baird, Spence	20
1948	Everett (condemns procedure)	5
1949	O'Brien, Pinck	3
1949	Powell, Powell	63
1950	Emmett, Hutchins, McDonald	76
1951	Howard, Buchtel	25

complaints and a thorough urological examination is indicated when the symptoms persist

Collar contracture of the bladder neck When symptoms of cystitis are accompanied by slowness of starting to urinate and lack of force of the stream, they are frequently due to collar contracture of the bladder neck This lesion should be ruled in or out whenever a female patient who has bladder symptoms is examined The presence of collar contracture of the bladder neck is the most frequent indication for transurethral resection of the vesical orifice

Etiology The embryological development of the bladder neck and urethra and consideration of the reasons for congenital causes of obstruction are well covered in the literature The excellent articles by Tourneau, Evatt, Trabucco, Johnson, Petrowa, Petrov, Caldwell and Folsom have adequately portrayed the embryology of the bladder, trigone, bladder neck, and male and female urethra It is the conclusion of these authors that the female urethra is the homologue of the posterior male urethra and prostate, potentially subject to pathological changes peculiar to the posterior urethra and bladder neck in the male

The cause of the collar contracture of the vesical orifice cannot always be determined Some are definitely congenital in origin Most of them, however, are congenital in predisposition with an acquired cause of onset of symptoms There may be an excessive number of periurethral glands which are hyperplastic at birth or which may undergo hyperplasia or may become infected in later life Abnormal thickening of the fibromuscular tissue at the vesical orifice is often congenital but may be asymptomatic until an acute infection, lowered resistance, or some other situation produces symptoms and aggravates the previously quiescent contracture Fibrous contracture of the vesical outlet is most often an aftermath of infection but may be entirely congenital in origin

Symptoms and findings Symptoms of obstruction in the female are not unlike prostatism in the male Obstruction should be suspected in all female patients with bladder discomfort, frequent urination, diminished urinary stream and the inability to empty the bladder completely Pain may be elusive and, as expressed by Cabot, within two feet of the urethra Varying amounts of residual urine may be present Since residual is a measure of a decompensating bladder, early or compensated obstruction may be overlooked if this one finding is used as a measure of obstruction Even though overflow incontinence or complete retention with large residuals may be present with varying degrees of urinary tract damage and azotemia, repeated urinalyses may reveal normal urine Recurrent or persistent pyuria is however the rule in these cases Varying degrees of cystitis and pyelonephritis may be the only guide to urinary obstruction The cardinal findings in establishing obstruction are residual urine, bladder trabeculation, cellules or diverticula or a collar contracture of the vesical neck seen on cystoscopy Actual obstruction may not be very noticeable on routine right angle cystoscopy but should and usually can be observed through the foroblique lens Further evaluation should be made by the retrograde lens and by digital palpation over the cystoscope sheath

Cystoscopic appearance through the right angle lens (fig 1, *A*) As the cystoscope is slowly withdrawn, viewing the trigone and then the bladder neck in sequence, the latter comes into view suddenly, rather than gradually, as is the case in the normal bladder In other words, the blur caused by the bladder neck being so close to the lens to be out of focus, occurs suddenly as the cystoscope is gradually withdrawn When the bladder neck is normal, this blur occurs gradually as the apex of the trigone fades into the bladder neck The appearance through the foroblique lens is similar, but the bladder neck looks higher than through the right angle lens (fig 1, *B*) Pseudopolypi are often found at the bladder neck just within the urethra An erroneous diagnosis of collar contracture of the bladder neck is more likely to be made when the foroblique lens is used because of the higher appearance of the bladder neck when viewed through the foroblique lens The retrograde lens is the best to use for making a diagnosis of collar contracture of the bladder neck (fig 1, *C*) The rim or collar can be seen plainly in the upper portion of the field, and there is a narrow shadow which is cast onto the trigone by the protrusion of the collar out into the bladder As the cystoscope is rotated, the collar-like protrusion can be seen surrounding the entire vesical outlet There is usually moderately severe subacute inflammation involving the collar and extending onto the bladder mucosa for a few millimeters Trabeculation is usually

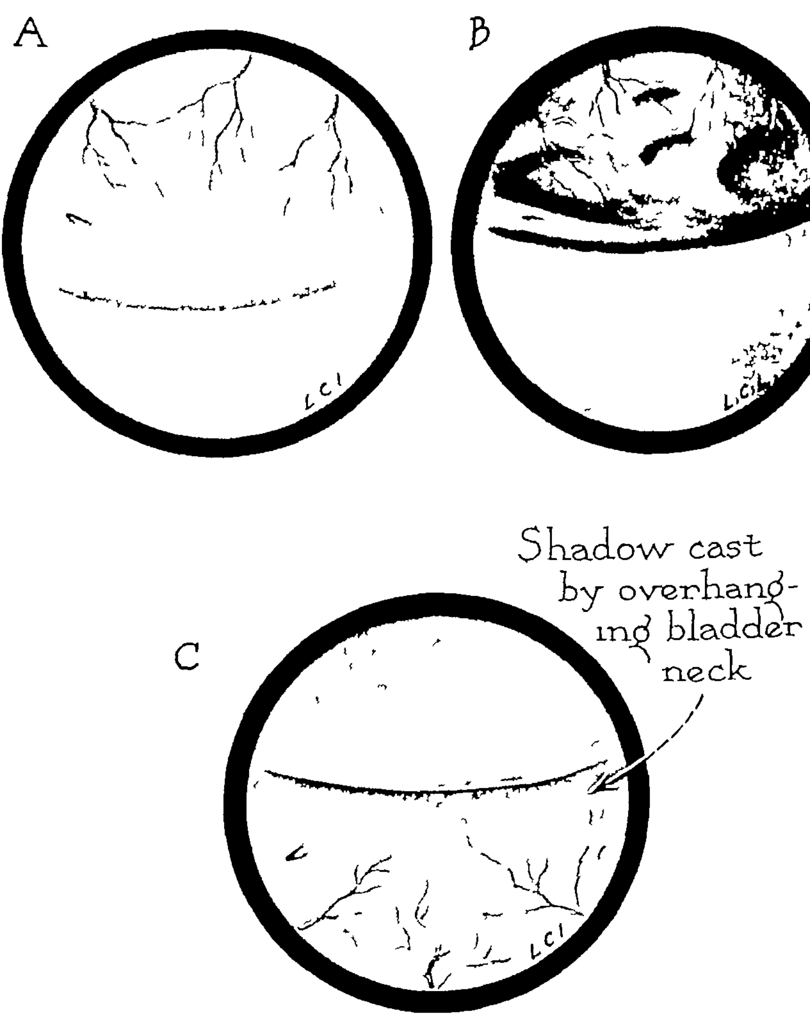


Fig 1 *A*, collar contracture of bladder neck in a woman as seen through right angle lens *B*, collar contracture as seen through foroblique lens *C*, collar contracture as seen through retrograde lens

found in the fundus of the bladder seen through either the right angle or the foroblique lens Sometimes it is marked and similar to the deep trabeculation seen in the male patient who has urinary obstruction due to an enlarged prostate

OTHER INDICATIONS FOR VESICAL NECK RESECTION

Pseudopolypi, granulation and severe chronic inflammation of the bladder neck which do not respond to local treatment may require bladder neck resection for definitive treatment When the patient's symptoms persist, and these lesions do not clear up after several months, treatment by sounds, application of 10 per cent silver nitrate solution to the bladder neck through an endoscope and other local treatment, transurethral resection of the mucosa and some muscle tissue usually relieves the symptoms and obliterates the pathological process

Neurogenic vesical dysfunction in women may respond favorably to bladder neck resection In our series the operation was done to relieve symptoms due to a central nerve lesion in 7 cases In this small group the results were good in two, improved in two, and there was no benefit in three None were made worse There was no increase in urinary incontinence in any Best results were obtained in patients who had a tight orifice and when there was a collar contracture as well as the neurogenic dysfunction

Conservative therapy is first indicated in most cases Urinary sedatives, antibacterial agents when needed, dilatation of the urethra with gradually increasing sizes of sounds, application of 10 per cent silver nitrate solution to the bladder neck on an applicator through an open tube endoscope and other local treatment may clear up the patient's symptoms and make vesical neck resection unnecessary

The discovery of a collar contracture of the vesical neck is not an indication in itself for transurethral resection When there are no symptoms or insignificant symptoms from this lesion, surgery for removal of the collar is not indicated

SURGICAL TECHNIQUE

The Stern-McCarthy electrotome is used by us Before starting the resection, a thorough survey of the bladder and bladder neck is made The ureteral orifices are identified and their proximity to the collar at the bladder neck is noted The resection is started at the 6 00 o'clock position on the bladder neck and successive pieces of tissue are removed up to the 12 o'clock position, first on one side, then on the other The loop is placed over the edge of the bladder neck and the inside end of the resectoscope is pressed firmly against the tissue The excursion of the loop must be short, not more than one half of a full length excursion Although it may be possible to resect the proximal third of the urethra without causing incontinence (Emmett, Hutchins and McDonald), it is usually not necessary to carry the resection out that far An area 0 5 to 1 0 cm wide extending entirely around the bladder neck is usually sufficient When the collar is large, a more extensive resection is necessary The deepness of the resection is one to four layers depending upon the thickness of the collar and the size of the pieces of tissue removed The coarse fibers of the bladder neck tissue must be exposed throughout the circumference of the bladder neck in order to adequately remove the collar When the resection is being done only to remove granulation tissue and pseudopolypi, the penetration is more superficial Observation with the retrograde lens is an aid in determining whether or not an adequate amount of intravesical tissue has been resected If there is a rim of tissue which casts a shadow (fig 2, *A*), this intravesical protrusion should be removed The finished resection should show the bladder neck to fade off gradually into the bladder wall (fig 2, *B*), no rim of tissue should be left

It is often difficult to determine the optimal limits of the resection The land-

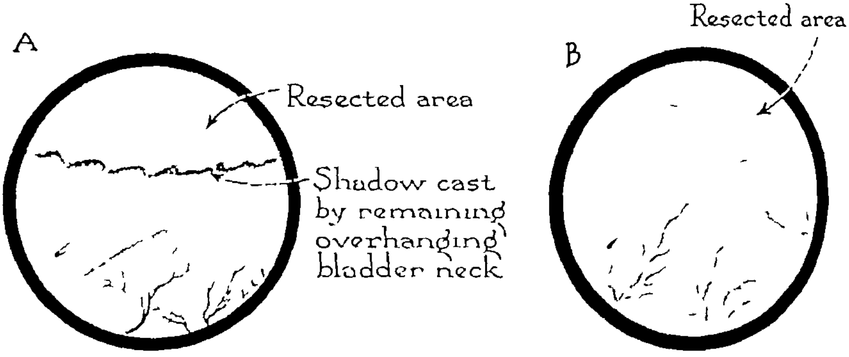


FIG 2 *A*, view through retrograde lens showing rim of collar remaining at bladder neck This should be removed *B*, view through retrograde lens showing edge of resected area after completion of resection There is no elevation of tissue between bladder and urethra

marks are much more indefinite than they are in the male prostatic urethra It is better to err on the side of conservatism and repeat the operation later if necessary, than to extend the resection too far out with resultant incontinence, too deep with resulting vesicovaginal fistula, or too high up with consequent injury to the ureteral orifices The latter mistake is avoided by frequently identifying the ureteral orifices during the operation

Followup care consists of keeping the bladder neck dilated while healing progresses A urethral sound is passed once a week beginning 2 weeks postoperatively A 24F sound is passed the first time, then the size gradually increased at subsequent visits until a 30F is passed It sometimes helps to use the Kollmann dilator with which the urethra can be eventually dilated to 40F if necessary When symptoms persist more than 3 months postoperatively, cystoscopy and urethroscopy are done If there is still some contracture or if excessive granulation or pseudopolypi are found, the resection of the bladder neck is repeated

REPORT OF CASES

Number (table 3) A total of 135 vesical neck resections were performed or supervised by the authors on 123 female patients for the 11-year period from 1945 to 1955 inclusive One resection was done on 115 patients, two were done on 7 patients and six resections were done on 1 patient

Age Table 4 shows that the majority of patients were in middle life In 6 patients who were less than 10 years old the lesion was congenital The histopathological study of the tissue from one of these revealed it to be identical with that of prostatic hyperplasia

Previous surgery (table 5) One hundred and six major surgical procedures had been done on these patients previous to the transurethral resection of the bladder neck Many of these operations were performed for the relief of the bladder symptoms There were, in addition to these, four patients who had previous pelvic irradiation, three for carcinoma of the cervix or uterus and one for endometrial polyps

TABLE 3 *135 resections were performed on 123 female patients*

Number of Resections Performed	On Number of Patients
1	115
2	7
6	1

TABLE 4 *Age distribution of female patients having transurethral resection of bladder neck—135 resections*

	Years of Age						
	0–4	5–9	10–19	20–39	40–59	60–79	80 or over
Number of cases	3	3	0	23	59	42	5

TABLE 5 *Major surgical procedures which had been performed previous to the vesical neck resection, 123 patients*

Surgical Procedure	No of Each Procedure
Hysterectomy	32
Appendectomy	18
Colporrhaphy	12
Oophorectomy	10
Rectal surgery	9
Cholecystectomy	7
Thyroidectomy	7
Herniorrhaphy	5
Uterine suspension	5
Urethroplasty Marshall Marchetti	1
	106

TABLE 6 *Symptoms complained of by 123 female patients who had transurethral resection of the bladder neck (most patients had several symptoms)*

Symptoms	Number of Patients Having Each Symptom
Frequency	117
Painful or burning on urination	104
Diminished urinary stream	103
Urgency of urination	79
Incontinence	33
Urgency incontinence	11
Overflow incontinence	10
Stress incontinence	10
Fistula	2
Hematuria	28
Acute urinary retention	28
Lumbar pain (renal?)	20
Enuresis	8

Symptoms (table 6) Most patients had the usual symptoms of frequency, urgency and burning on urination Diminished force of urinary stream was complained of by 103 of the 123 patients More than half the patients had had symptoms more than 5 years before vesical neck resection was done (table 7)

Cystoscopic diagnosis (table 8) Ninety seven of the 123 cases had a cystoscopic preoperative diagnosis of collar contracture of the bladder neck The vesical neck resection was performed for other lesions such as neurogenic bladder, granulation and pseudopolypi at the bladder neck and ectopic ureteral orifice in the posterior portion of the urethra

Neurogenic bladder (table 9) Seven patients had a diagnosis of neurogenic bladder due to a central nerve lesion In one of these—the patient who had six

TABLE 7 *Duration of symptoms before transurethral resection of the vesical neck was done*

Duration of Symptoms	No of Cases
Less than 1 year	25
1-2 years	12
3-5 years	20
6-10 years	28
More than 10 years	38
	123

TABLE 8 *Cystoscopic diagnoses and findings made preoperative to transurethral resection of the vesical neck in 123 female patients*

Cystoscopic Diagnosis	No of Cases
Collar contracture of vesical neck	97
Trabeculation and cellules	73
Pseudomembrane and granulation of trigone and bladder neck	54
Pseudopolypi at bladder neck	36
Chronic inflammation, hyperemia or incrustation	29
Cystocele	9
Interstitial cystitis	7
Vesical diverticulum	4
Vesicovaginal fistula	2
Ectopic ureteral orifice in posterior urethra	1
Irradiation cystitis	1
Papilloma of bladder	1
Septate bladder	1

TABLE 9 *Neurological diagnosis in seven female patients who had transurethral resection of the bladder neck for relief of neurogenic vesical dysfunction*

Neurological Diagnosis	No of Cases
Adhesive arachnoiditis (post spinal anesthetic)	2
Spina bifida	2
"Cord bladder"—paraplegia	1
Meningomyelocele (regional)	1
Multiple sclerosis (patient who had 6 resections)	1

TABLE 10 *Amount of residual urine, both pre- and postoperatively, in 135 transurethral resections of the bladder neck done on female patients Some of the final postoperative residuals were reduced after repeat resections*

Amount of Residual	Number of Cases	
	Before surgery	After surgery
Not recorded	61	60
None	23	58
1–99 cc	15	12
100–199 cc	9	2
200–499 cc	13	2
500 cc or more	14	1

TABLE 11 *Surgical procedures performed during the same hospitalization on 123 female patients who had transurethral resection of the bladder neck*

Surgical Procedure	No of Operations
Transurethral resection of bladder neck (123 patients)	135
Incision of trigone	7
Anterior colporrhaphy	5
Resection and/or electrocoagulation of ulcers in bladder	4
Nephrectomy (unrelated to the vesical lesion)	3
Urethroplasty	3
Excision urethral caruncle	2
Repair vesicovaginal fistula	2
Hysterectomy	1
Overlapping bladder wall for correction of hypotonia	1

TABLE 12 *Grams of tissue removed at each operation in 135 transurethral resections of the bladder neck in 123 female patients In 50 cases in which the pathology report gave no weight of tissue the report stated "several" to "30 pieces of tissue"*

	No Wt Given	Grams Removed									
		1 0	1 5	2 0	3 0	4 0	5 0	6 0	8 0	11 0	15 0
Number of patients	50	11	10	18	18	17	4	4	1	1	1

resections—the diagnosis of neurogenic bladder was not made until after the second resection was done even though thorough neurological examination had been made previous to the first resection

Preoperative infection Fifty-one of the patients had normal urinalysis preoperatively Fifty eight had recurrent pyuria and in fourteen there was persistent pyuria

Hydronephrosis Upper urinary tract study revealed varying degrees of hydronephrosis in 15 of the 123 patients Some of these were probably secondary to the bladder neck lesion

Residual urine (table 10) Although the presence of residual urine is an important indication for transurethral resection of the vesical neck in women, many patients who obtain excellent results from the operation have no residual

TABLE 13 *Pathological change found in tissue removed from bladder neck in 123 female patients Many had more than one pathological finding*

Pathology	No of Cases
Chronic inflammation (round cell infiltration)	96
Fibrosis (marked)	33
Squamous metaplasia	19
Glandular hyperplasia	18
Dilated vessels (granulation tissue)	10
Glands dilated with hyaline material	5
Normal bladder neck tissue	3
Adenocarcinoma	1
Amyloid	1
Fibromyoma	1
Hemosiderin	1

TABLE 14 *Complications occurring in 135 transurethral resections of the bladder neck in the female*

Immediate
  Hemorrhage
  Fever above 101°
Immediate convalescence
  Stress incontinence
  Vesicovaginal fistula (both repaired)
Remote
  Stress incontinence

TABLE 15 *Results of transurethral resection of the bladder neck in 115 female patients A followup report on 8 patients in the series*

	Immediate	Remote
Good (no symptoms)	56 (49%)	59 (51%)
Improved	49 (42%)	40 (35%)
Unimproved (condition same)	9 (8%)	13 (11%)
Worse	2 (2%)	3 (2%)

urine Characteristic obstructive symptoms and a cystoscopic diagnosis of coll contracture of the bladder neck are sufficient indication for resection even thoug no residual urine is found

Surgical procedures (table 11) Twenty-eight patients had surgical procedures in addition to the transurethral resection of the bladder neck which were per formed during the same hospitalization Some of these were done at the same time as the resection Most of them were performed to help correct the bladder symptoms of which the patient complained

Amount of tissue removed (table 12) The majority of patients had from 2 to 4 gm tissue removed at each operation The largest amount of tissue removed at a single operation was 15 gm

Pathology (table 13) Chronic inflammatory reaction was found in the majority

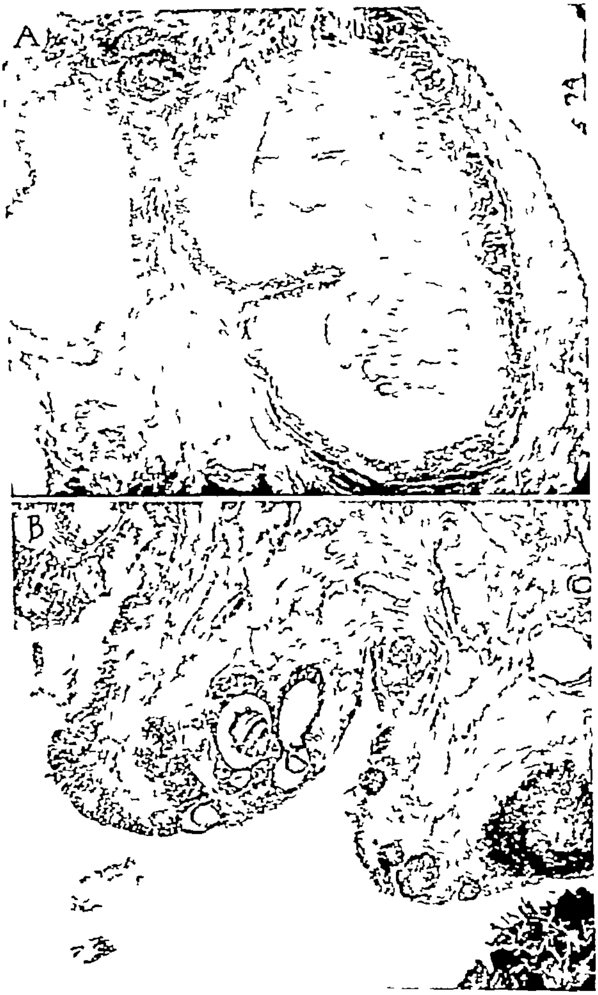


FIG 3 *A*, cystitis glandularis showing large glands lined by transitional and columnar epithelium × 90 *B*, squamous metaplasia, nests of Brunn beneath surface epithelium, cyst formation × 100

of specimens of tissue removed Glandular hyperplasia, or the typical "female prostate" was found in 18 of the 123 patients Therefore, less than 15 per cent of patients in this series had the transurethral resection of the bladder neck for relief of symptoms due to a true "female prostate" One of these patients was 3 years old

Figures 3 to 5 show the characteristic histopathological appearance of the different types of lesions found in the tissue removed from the bladder neck in the female

Complications (table 14) Hemorrhage severe enough to require aspiration of clots was the most frequent immediate complication Stress incontinence occurred in 9 patients during the immediate convalescence In four of these the patient

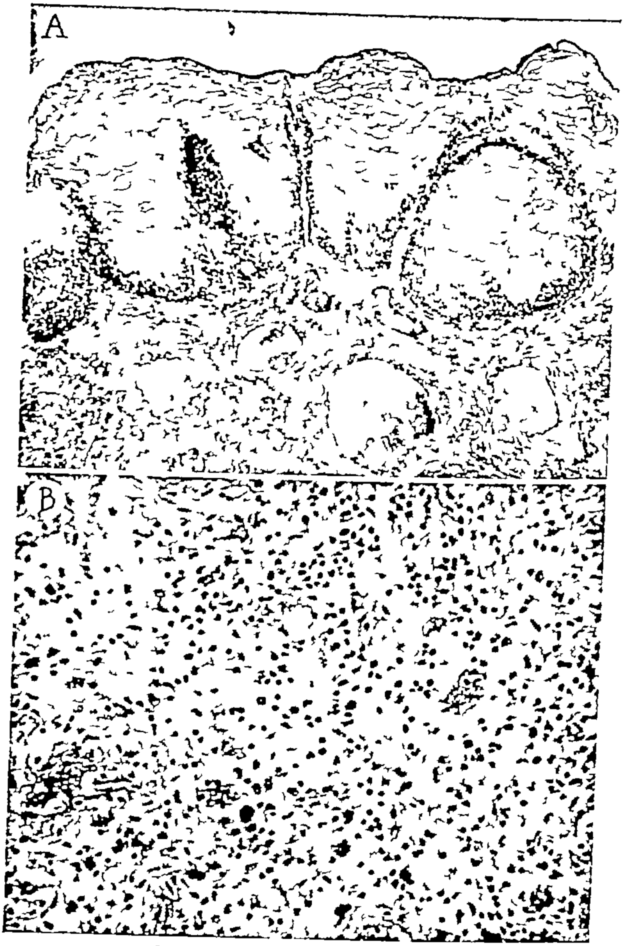


FIG 4 *A*, squamous metaplasia, glandular metaplasia with chronic inflammatory cell infiltration × 98 *B*, chronic inflammation × 300

gradually regained control of the urine and in one a urethroplasty was done The other four continued to have stress incontinence Vesicovaginal fistula occurred in 2 patients as a result of the transurethral resection of the bladder neck The fistula was closed in each by the first attempted repair through the vaginal approach

Results (table 15) One half of the patients were without bladder symptoms after healing was complete A little more than a third were improved, but still had some bladder symptoms Even though these patients were not cured of their bladder trouble, the operation was worthwhile Thirteen patients (11 per cent) had the same symptoms 6 months following surgery as they had before Four of these reported improvement during the first few months, then their old symptoms gradually recurred so that there was no permanent benefit The 3 patients who continued to be worse following surgery all had stress incontinence One of

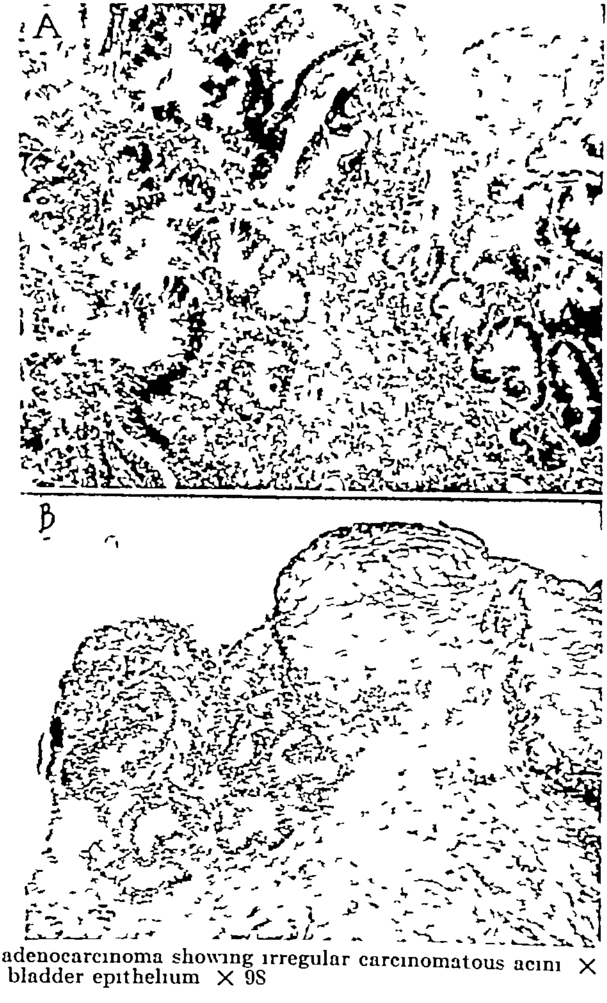
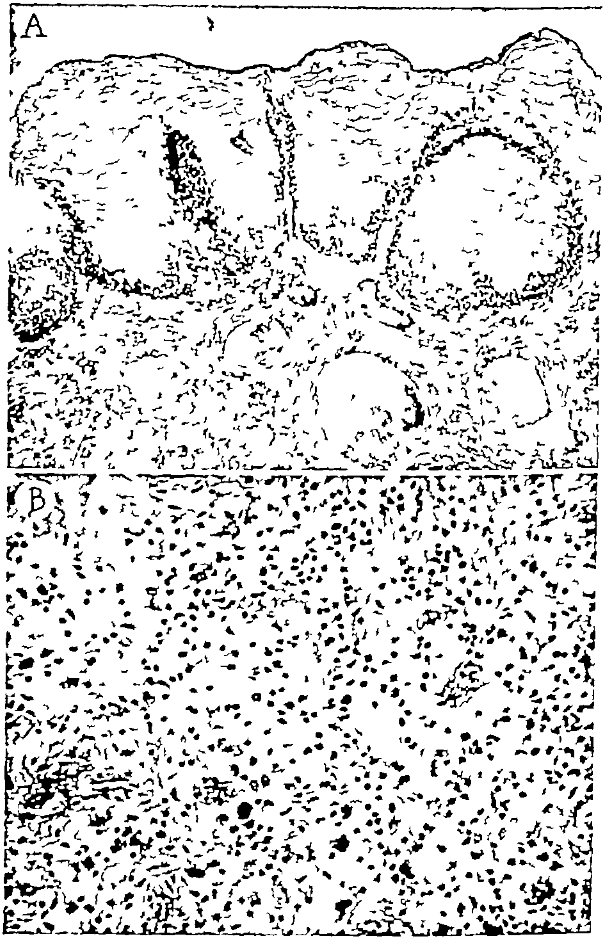


Fig 5 *A*, adenocarcinoma showing irregular carcinomatous acini × 98 *B*, squamous metaplasia of bladder epithelium × 98

the four whose stress incontinence persisted (table 14) had the same trouble previous to surgery and was counted as unimproved rather than worse

SUMMARY AND CONCLUSIONS

Transurethral resection of the bladder neck is indicated in the female patient when she has frequency, urgency, pain in the urethra, diminished urinary stream, when a collar contracture of the vesical orifice is found by cystoscopic examination and when conservative treatment has failed Sometimes the operation is indicated for removal of excessive granulation or pseudopolypi at the bladder neck Vesical dysfunction due to a central nerve lesion may be reduced in some cases by transurethral resection of the vesical orifice The surgical technique is not as definitely defined as that of prostatic resection Repeated operations are preferable to removing too much tissue too extensively the first time



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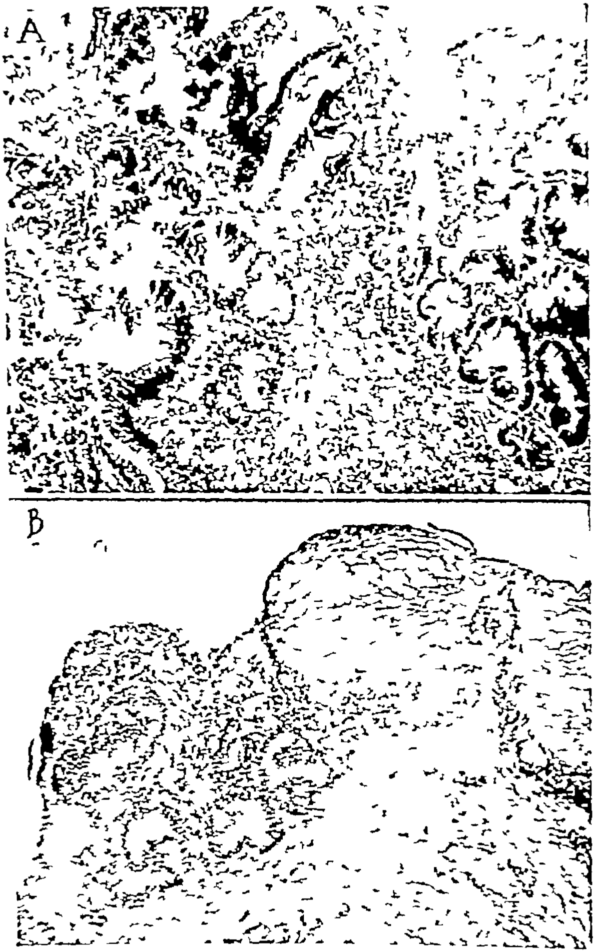

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A statistical summary of 135 resections on 123 female patients shows results which are not perfect but which are good enough to warrant continuing the operation in selected cases

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SIMULTANEOUS STUDIES OF THE EFFECT OF VARIOUS CHOLINERGIC AND ANTICHOLINERGIC DRUGS ON END ORGANS OF THE AUTONOMIC NERVOUS SYSTEM STOMACH, COLON, AND URINARY BLADDER

JOHN W DRAPER, MIECZYSLAW SIERP AND OSWALDO KARAM

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We have studied the effect of the cholinergic and anticholinergic drugs on the genitourinary system during the past 4 years A reliable method for assaying the action of these agents on the detrusson muscle of the bladder has been reported[1, 2, 3] We have also demonstrated the effect of these drugs on the ureter by recording the action potential with an amplifier and an oscillograph[2] Numerous observers have reported on the response of the colon and stomach to these agents

Clinical observations have suggested that these drugs may have a selective action on one or more organs innervated by the autonomic nervous system We have felt it would be very useful from a therapeutic point of view to establish definitely whether any of these agents would suppress gastric secretion and acidity without interfering with the detrusor action of the bladder or vice versa It would also be of use to know whether the contractions of the sigmoid could be slowed without suppressing the activity of the parasympathetic system on the upper gastrointestinal tract In order to investigate this problem we have set up an experiment to record simultaneously the action of ten* anticholinergic and cholinergic compounds on the stomach, colon, and urinary bladder Other side effects of these agents were not measured quantitatively and therefore were not recorded in these experiments

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[1] Draper, John W , Wolf, Stewart, Murphy, J F and Kravetz, Howard The effect of banthine in the treatment of genito urinary disorders J Urol , 69 632-640, 1954

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SC 3171 (Pro-Banthine) (Searle) Beta di isopropylaminoethyl xanthene 9 carboxylate methobromide
Compound U 0229 (Upjohn) alpha, alpha diphenyl gamma 1 piperidylbutyramide hydrochloride
Compound U 0382 (Pamine) (Upjohn) Epoxytropine tropate methylbromide
Compound WIN-4369 (Winthrop Stearns) 2 diethylaminoethyl 2 cyclopentyl 2 (2 thienyl) hydroxyacetate methobromide

PROCEDURE

The selection of suitable subjects for this experiment is important since their co-operation is necessary to obtain accurate results A nasal tube, rectal tube and urethral catheter are not designed to contribute to a patient's peace of mind and several of our experiments were discontinued for this reason The experiment is tedious for the patient since observations are taken for 2 hours, 1 hour without medication to establish a true baseline ½ hour of observation of the response to the anticholinergic agents and ½ hour for the cholinergic The patients selected were placed on nothing by mouth for 12 hours prior to the experiment Two hours before the experiment tap water enemas were given until the return flow was clear One hour prior to the experiment a Levine tube was introduced and its contents were aspirated and discarded A second Levine tube with a soft rubber balloon at its distal end was introduced through a proctoscope into the sigmoid and inflated with 70 cc air This tube was then connected to a U-shaped glass tube with a displaceable column of water and a floating kymograph pen to record the motility of the sigmoid A No 18F 5 cc Foley catheter was then introduced into the bladder The bladder was emptied and 100 cc normal saline solution was introduced slowly into the bladder The catheter was then connected to a simple water manometer and readings of intravesical pressure were taken and recorded every 5 minutes At the same time the sigmoid motility was recorded continuously on the kymograph During this hour while the bladder readings and record of the sigmoid motility were proceeding gastric secretion was obtained from the stomach every ten minutes The volume of secretion, the pH and the units of free acid were determined later At the end of this hour which we call the control period the anticholinergic drug was administered parenterally Readings of the bladder contractions and sigmoid motility and determination of gastric secretion were observed for a thirty minute period At the end of this second period of observation one and one-half hours since the beginning of the experiment 5 mg furmethide, a potent cholinergic agent was injected subcutaneously Observations were continued and specimens were obtained for a thirty minute interval

Figure 1 illustrates the simultaneous recording of the sigmoid motility the cystometrogram free acid of the gastric secretion, the pH of the gastric secretion and the volume in cubic centimeters of each aspiration A satisfactory baseline for each observation was obtained during the hour of preliminary observation Unfortunately this patient did not secrete a sufficient amount of free acid to have its determination of any clinical significance

Within five minutes after the injection of 50 mg of the anticholinergic compound, banthine, there was a significant drop of 2 cm in the intracystic pressure The pressure remained at this level during the 30-minute observation period before the injection of furmethide The kymograph tracing showed that the waves of sigmoid motility were markedly reduced following the intramuscular injection of the 50 mg banthine and this inhibition of motility persisted throughout the 30-minute interval The volume of gastric secretion which prior to the

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SIMULTANEOUS STUDIES OF THE EFFECT OF VARIOUS CHOLINERGIC AND ANTICHOLINERGIC DRUGS ON END ORGANS OF THE AUTONOMIC NERVOUS SYSTEM STOMACH, COLON, AND URINARY BLADDER

JOHN W DRAPER, MIECZYSLAW SIERP AND OSWALDO KARAM

From Department of Surgery (Urology), Cornell University Medical College and Second (Cornell) Division Urology, Bellevue Hospital, New York, N Y

We have studied the effect of the cholinergic and anticholinergic drugs on the genitourinary system during the past 4 years A reliable method for assaying the action of these agents on the detrussor muscle of the bladder has been reported[1, 2, 3] We have also demonstrated the effect of these drugs on the ureter by recording the action potential with an amplifier and an oscillograph[2] Numerous observers have reported on the response of the colon and stomach to these agents.

Clinical observations have suggested that these drugs may have a selective action on one or more organs innervated by the autonomic nervous system We have felt it would be very useful from a therapeutic point of view to establish definitely whether any of these agents would suppress gastric secretion and acidity without interfering with the detrusor action of the bladder or vice versa It would also be of use to know whether the contractions of the sigmoid could be slowed without suppressing the activity of the parasympathetic system on the upper gastrointestinal tract In order to investigate this problem we have set up an experiment to record simultaneously the action of ten* anticholinergic and cholinergic compounds on the stomach, colon, and urinary bladder Other side effects of these agents were not measured quantitatively and therefore were not recorded in these experiments

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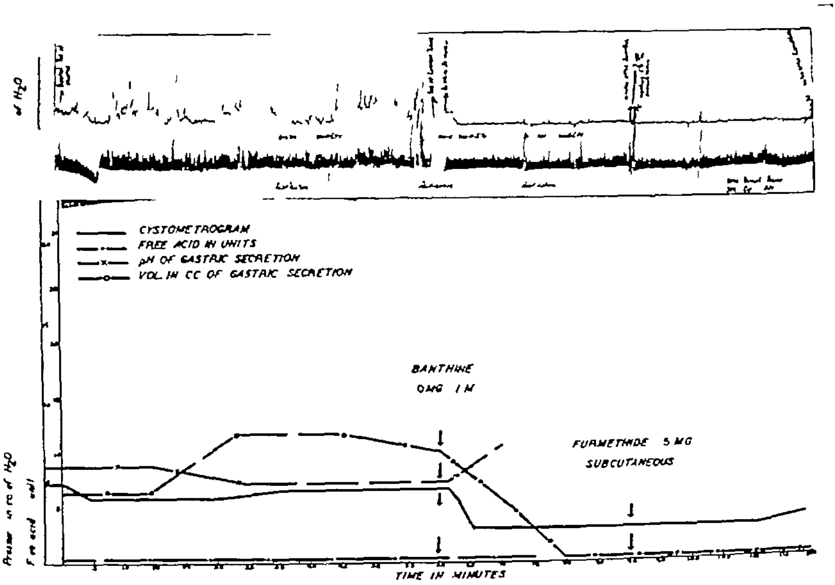

FIG 1

administration of banthine had varied between 8 and 12 cc with each aspiration diminished 10 minutes after the injection of banthine to 5 cc and 20 minutes later no gastric secretion could be obtained The pH of the gastric secretion which was fairly well stabilized at 5 prior to the injection rose to 7 within 10 minutes and within 20 minutes no further observations could be made because the gastric secretion disappeared entirely after this time Free acid, as has been noted, was absent during the entire experiment

After the anticholinergic effect of the intramuscular banthine had been observed and recorded for ½ hour 5 mg of the cholinergic agent, furmethide was injected subcutaneously No increase in the sigmoid motility resulted There was also no significant change in the cystometrogram No gastric secretion was obtained and for this reason no observations could be made of the pH or of the free acid

Figure 2, *A* illustrates the effect of pamine (U-0382) on sigmoid motility, gastric secretion and the intravesical pressure of the urinary bladder During the observation period the sigmoid motility was demonstrated by the usual pattern of bowel contractions The intravesical pressure remained between 5 and 6 cm of water The volume of gastric secretion which was determined at 10-minute intervals fluctuated between 10 and 12 cc The free acid content of this secretion was between 30 and 31 units on each aspiration The pH of the gastric secretion remained at 2 5 during the observation period

Following the intramuscular injection of 30 mg pamine there was a suppression of contractility of the sigmoid (numerous artifacts were recorded by the kymograph) There was a slight fall of the intracystic pressure from 5½ cm to 4½ cm The volume of gastric secretion dropped from 10 cc at each aspiration to 4 cc at

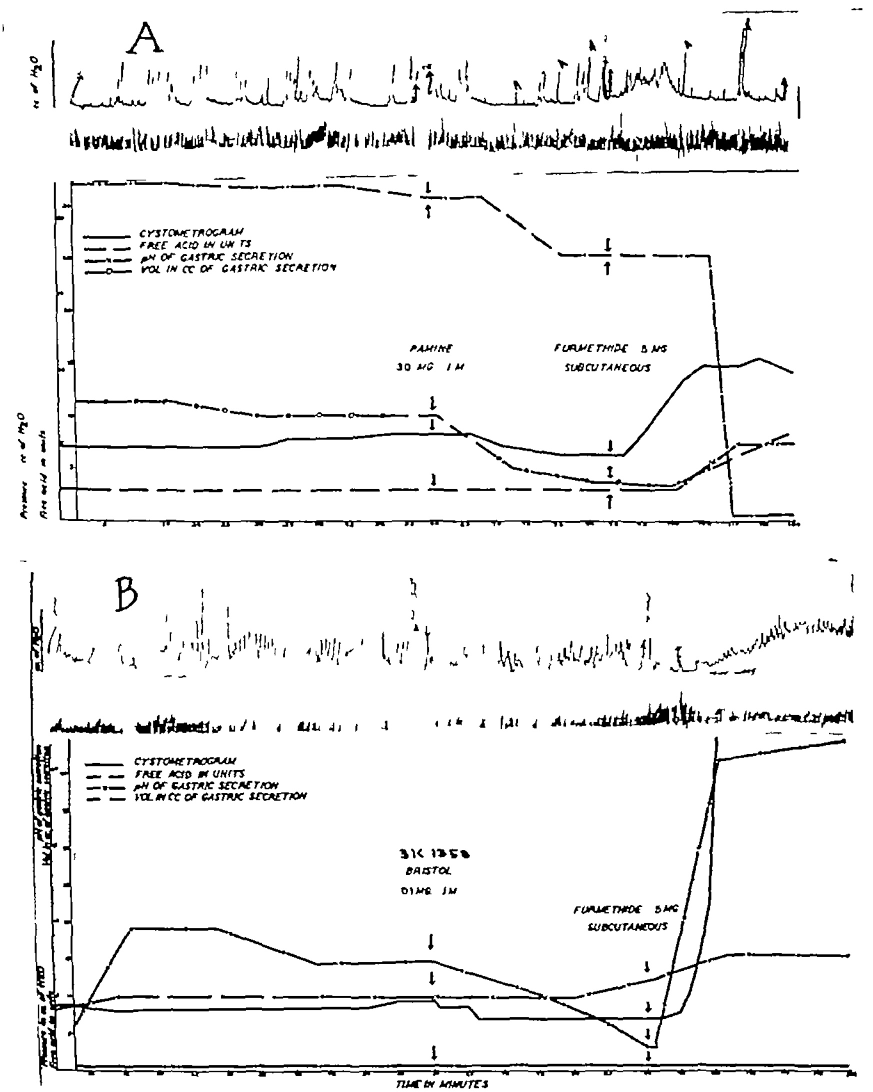

Fig 2

the end of the pamine test period The pH of the gastric secretion was 2 5 The free acid fell from 30 units to 24 units during this half hour observation period

Within 5 minutes after the subcutaneous injection of 5 mg of furmethide there was a marked rise in the baseline of the sigmoid pattern There was also an increase in the frequency of the sigmoid contractions These contractions were irregular for the next ten minutes and then gradually subsided The free acid in the gastric secretion dropped from 24 to 0 in 20 minutes after the injection of the furmethide The intracystic pressure rose from 4 5 cm of water to 10 cm The pH of the gastric secretion increased from 3 to 7 cc in the last specimen

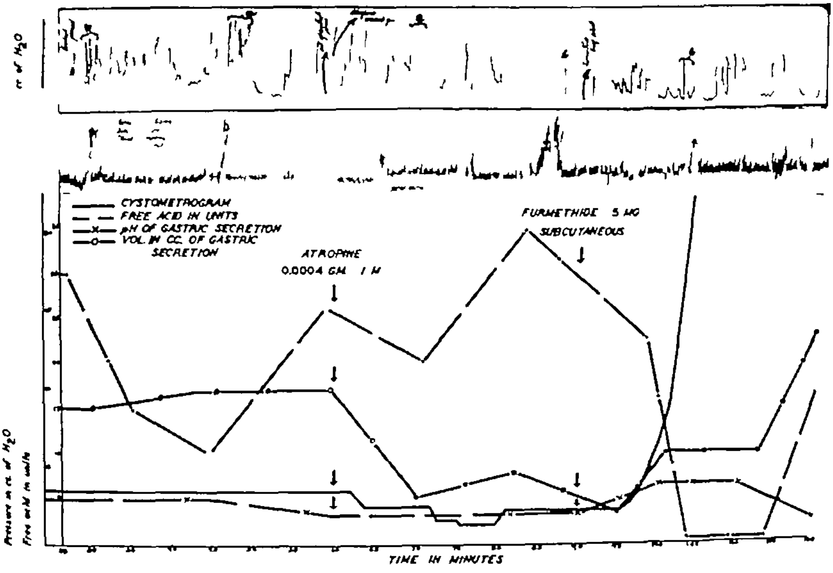

FIG 3

Figure 2, *B* records our findings in a similar experiment The sigmoid motility, cystometrogram, and the gastric secretion were studied for the 1-hour period Again we note the normal pattern of sigmoid motility The volume of gastric secretion varied from 7 to 18 cc The pH of the gastric secretion remained quite fixed at 5 The cystometrograms showed no significant change Following the intramuscular injection of 0 1 mg centrine there was some slight decrease in the frequency and amplitude of contractions of the sigmoid and lowering of the baseline The cystometrogram showed a drop in pressure from 4 to 3 cc The pH of the gastric secretion dropped from 12 to 3 cc at the end of the ½ hour period

Following the injection of 5 mg of furmethide subcutaneously there was a rise in the intrasigmoid baseline pressure The amplitude of the contractions first decreased and then returned almost to the pre-furmethide levels There was a rise in the water level in the cystometer from a baseline of approximately 4 cm to 25 cm within ten minutes after the injection of furmethide The volume of gastric secretion also rose from 3 cc to 40 cc within ten minutes A subsequent rise in the next twenty minutes to 49 cc was noted The pH of the gastric secretion rose from 6 to 8 There was no free acid in this patient's gastric content

Figure 3 demonstrates the results obtained in a similar study comparing the action of atropine and furmethide It should be noted that because of technical difficulty with the kymograph only the last 35 minutes of the observation period are illustrated The sigmoid motility was demonstrated by a very irregular pattern throughout this experiment Long contractions with high amplitude and an elevated baseline were noted During the control period the volume of gastric secretion remained between 16 and 18 cm The free acid fluctuated between 20 and 10 units At the end of the observation period free acid reached 26 units

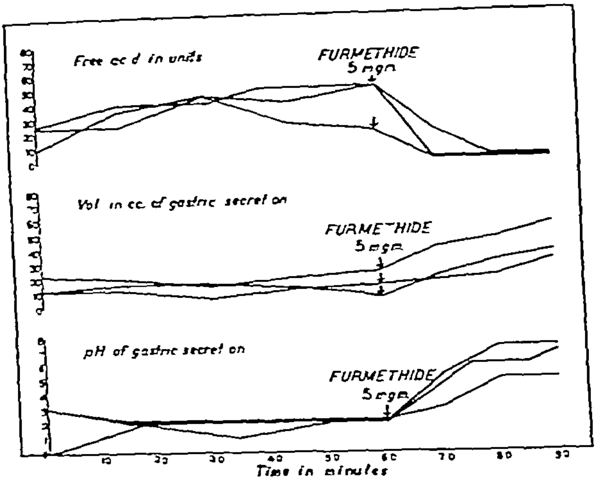

FIG 4

The pH of the gastric content fell from 2 5 to 2 The fluid level in the cystometer remained at 4 cm during the entire control period

Following the intramuscular injection of atropine 0 0004 gm no significant changes appeared in the pattern of the sigmoid motility The volume of gastric secretion fell from an average of 15 cm per aspiration to 5 cm The free acid content of the gastric secretion rose to 35 units within 25 minutes after the atropine injection and the pH of the gastric secretion remained fixed at 2 5 throughout this period of the experiment

Following the subcutaneous injection of 5 mg furmethide there were no very significant changes in the sigmoid motility There was, however, a very marked rise in the intravesical pressure from 2 5 to 23 cm in 10 minutes The volume of gastric secretion rose at each aspiration from 5 to 23 cm in 25 minutes The free acid of the gastric secretion fell from 30 units to 0 in 15 minutes It remained at zero for 10 minutes, then rose to 16 units at the last aspiration

In addition to the compounds illustrated we have used pro-banthine, antrenyl, U-0229, WIN 4369, and profenil which also demonstrated only quantitative differences in their potency without affecting selectively a particular end organ in the bladder, stomach or colon These compounds in addition to those illustrated also demonstrate only minor variations in the response of the stomach, colon, and bladder There are quantitative differences in their potency

In reviewing the over-all effect of these anticholinergic agents it appears that there are only minor variations in effectiveness of these drugs on the stomach, bladder and colon In other words if an agent is able to inhibit the motility of the sigmoid it also reduces the detrussor tone, decreases gastric secretion and lowers the units of free acid In reviewing these results we found that in three of our patients following the injection of furmethide there was a sharp fall in the units of free acid present in the gastric secretion although there was an increase in the secretion of gastric juice We thought it advisable to investigate further this observation and therefore passed nasal tubes on three additional patients just for the purpose of studying their gastric secretion following the administration of furmethide In each case it was noted that following the injection of 5 mg of this drug there was a rise in the total output of gastric juice as is demonstrated in figure 4 There was a decrease in each case in the free acid present and a rise in the pH of the gastric content

CONCLUSION

It appears to us from this study that there is very little evidence of selective action of the drugs which we have observed on the stomach, bladder, or sigmoid

It is interesting to note that furmethide will produce an increase in the pH and the volume of gastric secretion and a sharp decrease in the free acid in the gastric juice Further investigation of this effect should be carried out *

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UROLOGIC PROBLEMS IN SPINA BIFIDA

HERBERT C KENNEDY* AND CLARENCE V HODGES

From the Division of Urology, Department of Surgery, University of Oregon Medical School, Portland, Oregon

The association of spina bifida and malformations of the spinal cord and its coverings with neurogenic dysfunction of the urinary tract is now well recognized Although the survival rate of these children in the past was quite low, in recent years use of antibiotics and improvements in neurosurgical, urologic, and orthopedic procedures have resulted in a much better outlook

No attempt will be made in this presentation to outline the neuroanatomy of the bladder or the pathologic neurophysiology involved in the production of neurogenic vesical dysfunction in cases of spina bifida These have been adequately described in other publications [1] [2]

MATERIAL

Twenty-seven patients with spina bifida and associated urologic problems have been seen at the University of Oregon Medical School Hospitals and Clinics since July 1, 1948 The group includes 14 males and 13 females, ranging in age from 1½ to 34 years, the average age being 8 years Excepting one 34-year-old man, all patients were under 16 years of age

The site of the spina bifida was in the cervical region in one patient, lumbar in 4, lumbosacral in 18, and sacral in 4 patients Fourteen patients had meningocele and 13 had meningomyelocele All but 5 have had surgical repair of the meningocele or meningomyelocele There were no instances of spina bifida occulta in this series Sixteen patients had partial paralysis of the lower extremities, 6 were totally paraplegic, and 5 had no significant motor involvement of the lower extremities Associated congenital anomalies included hydrocephalus, 5 cases, club feet, 10 cases, congenital dislocation of the hips, 6 cases, and bilateral undescended testes, 1 case

All patients had incontinence of urine, this was the chief complaint in most cases Several also gave histories of recurrent chills, fever, and pyuria

The urological workup included 1) complete urinalysis with Gram stains and cultures, 2) residual urine determinations, 3) cystograms, helpful in demonstrating trabeculation, diverticula and, of considerably more importance, the presence or absence of vesicoureteral reflux, 4) cystoscopy, helpful in determining the amount of bladder inflammation, the presence of trabeculation or cellule formation, and in visualizing contractures of the vesical neck, 5) cystometry, of marked value in demonstrating the relationship of intravesical pressure to volume, pres-

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Read at annual meeting of Western Section of American Urological Association, San Francisco, Calif April 30–May 3, 1956

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ence or absence of reflex contractions of the bladder and strength of the contractions, the maximum voluntary pressure produced by straining and the bladder capacity, 6) excretory urography, to demonstrate renal function and anatomical configuration of the kidneys In many cases retrograde urography was also done, particularly when reduced renal function resulted in non-visualization

INITIAL STATUS

Eighteen patients had significant urinary tract infections when first examined, in two additional cases infection developed while the patients were undergoing treatment Only three had no residual urine Eight patients had up to 50 cc residual urine, 16 had more than 50 cc residuum, 12 of these had more than 100 cc residual urine Definite trabeculation of the bladder was found in 17 patients Twelve patients had definite vesical neck contracture seen at cystoscopy, 15 had no demonstrable vesical neck contracture, although many of these had significant amounts of residual urine and, presumably, had functional bladder neck obstruction without anatomic evidence of contracture Recurrent decubiti were serious problems in 4 patients, constant soiling with urine as a result of incontinence was an important contributing factor

Sixteen patients had normal-appearing upper urinary tracts Eight patients demonstrated both vesicoureteral reflux and hydronephrosis, unilateral in 3 patients and bilateral in 5 patients Three patients showed hydronephrosis without demonstrable reflux, in 2 patients this was unilateral and in 1 case it was bilateral In no case was there reflux without associated hydronephrosis

It is apparent that the patients with neurogenic dysfunction of the urinary tract secondary to spina bifida present four important problems 1) obstruction (a, at the bladder neck, b, at the ureterovesical junction and/or urinary reflux), 2) infection, 3) impaired renal function resulting from the effects of both obstruction and infection, 4) incontinence

AIMS IN THERAPY

There are four chief objectives to be accomplished in the treatment of these patients These are listed in the order of their priority, which is identical with the sequence which seems most logical for attacking them These objectives are 1) preservation and restoration of renal function, 2) elimination of residual urine, 3) elimination of infection, 4) establishment of satisfactory urinary control

METHODS OF TREATMENT

Urinary diversion A Indwelling urethral catheter Preservation and restoration of renal function are usually initiated by urinary diversion by means of indwelling urethral catheter, benefits obtain from obviation of bladder neck obstruction, lessening of ureteral reflux and incidental to these, reduction of infection This method was used as a temporary measure at one time or another during the care of most of these patients The following case history is a good example of how the kidneys may be protected by continuous drainage of the bladder with a catheter

Case 1 J A M , a 9-year old girl with lumbosacral spina bifida and meningocele, was first seen in February 1954 The bladder showed marked trabeculation

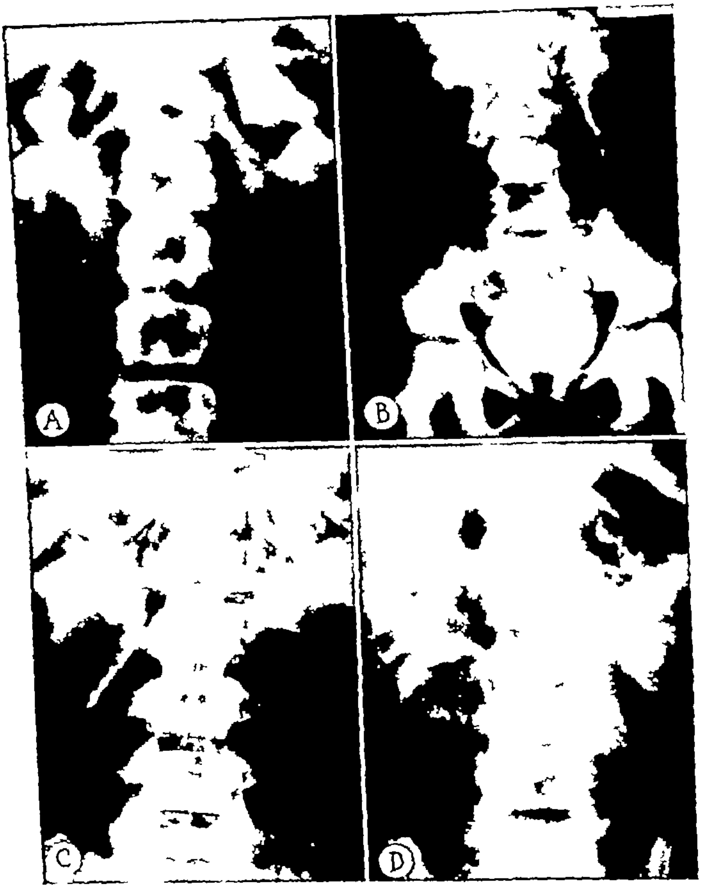

FIG 1 J A M A, excretory urogram on admission shows bilateral hydronephrosis B, excretory urogram, after drainage by indwelling urethral catheter for 3 months, shows decreased dilatation of urinary tracts bilaterally C, excretory urogram, 3 months after indwelling catheter had been removed, shows progression of hydronephrosis bilaterally D, 3 months later, after catheter drainage had been resumed, excretory urogram again shows improvement of both kidneys

and contained 450 cc residual purulent urine There was no demonstrable bladder neck contracture Upper tract studies showed bilateral ureteral reflux with marked hydronephrosis and hydroureter (fig 1, *A*) The patient was maintained on continuous urethral catheter drainage for 17 months Excretory urography in May 1954 and October 1954 (fig 1, *B*) showed decreased dilatation of the upper urinary tracts bilaterally Bilateral ureteral reflux persisted In November 1954, a Hutch type plastic operation was done on the left ureterovesical junction In February 1955, a Vest type ureteroneocystostomy was done on the right side In July 1955, a transurethral resection of the vesical neck was performed The patient was sent home without a catheter for a period of 2 months She voided well and had good control both day and night In September 1955 she had suprapubic pain and cloudy urine and again became completely incontinent She was readmitted to the hospital in October 1955 after a period of 3 months without catheter drainage Excretory urograms showed a [illegible] f hydronephrosis bilaterally (fig 1, *C*) A cystogram demonstrated no ureteral reflux The patient was again placed on catheter drainage for a period of 3 months, when readmitted to the hospital in January 1956, excretory urography again showed marked improvement in the appearance of both kidneys (fig 1, *D*) A second transurethral resection of the vesical neck was done and the patient was sent home with good control and absence of residual urine

B Nephrostomy The results of a questionnaire by DeVries[3] indicated that 48 per cent of those answering felt that nephrostomy was the operation of choice in hydronephrosis and hydroureter due to spina bifida This procedure can be life-saving in far advanced cases of renal damage but was not used in this series

C Ureterosigmoid anastomosis and sigmoid colostomy, forming a "wet colostomy," has been advocated by some writers[4] but has many disadvantages This procedure was not done on any of this group

D Implantation of the ureters in an isolated ileal segment has been done by some workers[5] with satisfactory results Failure of methods designed to achieve urinary control would furnish the chief indication for this form of diversion

E Permanent cystostomy is an excellent procedure when permanent urinary diversion seems indicated This operation was performed on only one patient in this study, an adult male with bilateral hydronephrosis and progressive renal damage

Prevention of vesicoureteral reflux has been achieved by ureterovesical plasty or ureteroneocystostomy The methods described by Hutch[6] and by Vest were each performed on three ureterovesical junctions In the Vest procedure the ureter is reimplanted in the bladder with its terminal portion everted so as to form a nipple projecting into the bladder Theoretically this nipple is compressed during bladder filling and thus prevents reflux

An "intussusception" procedure (suggested by Dr W E Goodwin) was also performed on three ureterovesical junctions This procedure was done by "intussuscepting" the terminal 2 cm of ureter into the bladder without reimplantation of the ureter, in such a way as to form a nipple projecting into the bladder lumen This procedure is similar to that of Vest except that the ureter is not reimplanted

The nine aforementioned operations were performed on 5 patients and thus far no postoperative evidence of ureteral reflux has been found

Transuretero-ureterostomy was done in one instance with gratifying results

Case 2 M C, a 5-year old girl, had a lumbosacral spina bifida with meningocele which had been repaired at the age of 4 weeks She was a partial paraplegic and had been incontinent of urine since birth She was first seen in June 1955, at which time she had mild trabeculation of the bladder with 50 cc of residual urine There was marked pyuria Urographic study showed minimal caliectasis on the right, the left ureter and kidney showed ureteral reflux with hydronephrosis and hydroureter (fig 2, *A*) In July 1955, left ureterolysis and ureteroneocystostomy were undertaken, however, after detaching the dilated and tortuous ureter at the bladder and freeing it up toward the kidney, too vigorous traction resulted in its

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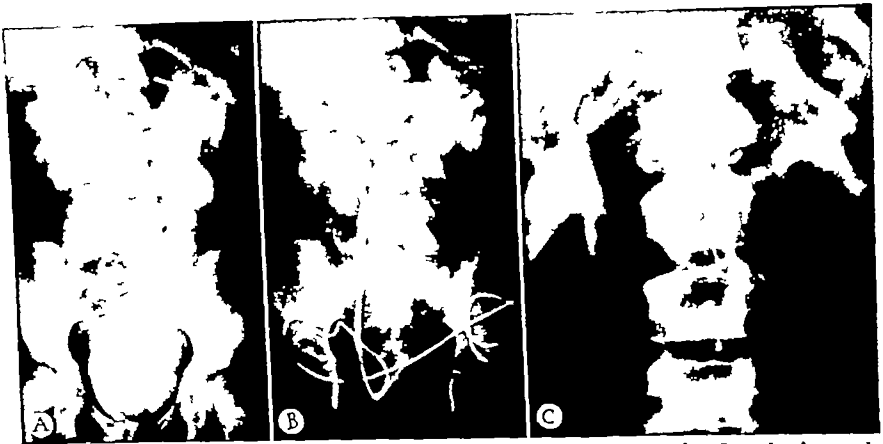

FIG 2 M C *A*, cystogram on admission shows left vesicoureteral reflux, hydronephrosis and hydroureter *B*, postoperative retrograde urogram shows splinting catheters in place after transuretero ureterostomy, with end to side anastomosis of proximal left ureter to right ureter *C*, excretory urogram 3 months after transuretero ureterostomy shows improved appearance of both kidneys, particularly left

avulsion about 3 cm below the renal pelvis The proximal left ureter was led across through a retroperitoneal tunnel to be anastomosed in end-to-side fashion to the right ureter (fig 2, *B*) The patient made an uneventful recovery In November 1955, excretory urography (fig 2, *C*) showed marked improvement in the appearance of both kidneys, particularly the left

Elimination of residual urine A Ureterolysis and partial ureterectomy, consisting of mobilizing and shortening tortuous dilated ureters, which were then reimplanted in the bladder, were carried out to varying degrees during the plastic operations on the ureterovesical junctions described above

B Transurethral resection of the vesical neck was performed 18 times on 13 patients in this study In 10 of these residual urine was eliminated or reduced to insignificant amounts In 3 patients, satisfactory control resulted following relief of bladder neck obstruction by transurethral resection

Case 3 M S , a 10-year old boy, had lumbosacral spina bifida and a meningocele which had been repaired at the age of 6 months He was totally incontinent of urine and the bladder contained 300 cc residual urine His urine was clear and culture was negative Urograms demonstrated absence of ureteral reflux and normal upper urinary tracts except for dilated distal ureters Cystoscopic study revealed contracture of the vesical neck Following transurethral resection of the bladder neck, there was no residual urine and the patient remained dry as long as he voided every two hours

C Vesicourethroplasty The plastic operation on the bladder neck, described by Bradford Young,[7] was performed on 2 patients A vertical incision was made through the bladder neck and adjacent prostatic urethra and this incision was closed transversely to provide a larger bladder neck The Bonnin operation,[8] in which a Y incision is made at the bladder neck and closed as a V, was performed on one patient Residual urine has been decreased or eliminated in these three patients

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Elimination of infection After elimination of obstruction and urinary stasis vigorous attempts were made to decrease the amount of infection by means of antibiotics or chemotherapeutic agents In some instances, chronic infection has persisted in spite of the most intensive therapy, presumably because of extremely drug-resistant strains of bacteria

Establishment of control Satisfactory control was accomplished in 7 patients in this study by means of anticholinergic agents or rectus fascial transplants or both This subject is a lengthy topic in itself and will be discussed in detail in a future paper on the subject

SUMMARY

Our experiences with the urologic problems of 27 patients with spina bifida have been presented The problems presented include 1) obstruction, 2) infection, 3) impairment of renal function, 4) incontinence It has seemed logical to attack these problems in the following order 1) measures intended to preserve and restore renal function, 2) elimination of residual urine, 3) elimination of infection, 4) attempts to establish urinary control

All the patients in this study were incontinent of urine and the majority (18) had infected urine The majority demonstrated trabeculation of the bladder Twenty-four of the 27 patients had varying amounts of residual urine, 16 having significant amounts of residuum Sixteen of the patients had normal upper urinary tracts and eleven demonstrated abnormal upper tracts The cystometric studies showed the autonomous type of neurogenic bladder to be the kind most commonly found in these patients

Permanent diversion of the urine by permanent cystostomy was employed in only one patient in this series Nine plastic operations on the ureterovesical junction were performed on 5 patients and transuretero-ureterostomy was done on 1 patient, resulting in elimination of ureteral reflux in all cases Eighteen transurethral resections of the bladder neck were performed on 13 patients, resulting in satisfactory reduction of residual urine in 10 patients and improved control in 3 patients Satisfactory control of urine was accomplished in 7 patients One patient is on permanent cystostomy drainage and another will remain on permanent urethral catheter drainage because of mental deficiency and decubiti There has been one death, at 21 months, of pneumonia and chronic pyelonephritis

Of the remaining patients, control of urine has not yet been attained in 17 patients Medical and/or surgical means have been tried in 6 cases with no success so far Definitive measures to gain control have not yet been carried out in the other 11 patients, in 2 cases because of persistent infection, in one case because residual urine has not yet been eliminated, and in the others either because they are yet too young or because procedures to correct residual urine have only recently been done

Seven patients have been rehabilitated to a point where they have satisfactory urinary control and are free of urinary stasis and infection These patients will require frequent observation to maintain this state

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ANTEPUBIC VESICO-ILEAL-NEOURETHROSTOMY

CHUJI KIMURA, NAOHIKO HARADA AND WATARU TATSUMI

From the Second Surgical Department of Kyoto University Medical School, Japan

In modern surgery, we rather frequently encounter patients who are suffering from organic or functional disturbances of the urinary tract due to defects in the posterior urethra or the neck of the urinary bladder caused by trauma, inflammation or neoplasm The surgical procedure for these cases is, however, so difficult that successful results are rarely observed Heretofore, an external urinary fistula or ureterocolostomy by Coffey's method has been devised for these patients

The anastomosis of the urethra with another hollow organ, for instance, the small intestine, which is interposed between the urethra and the urinary bladder for the reconstruction of a natural urinary tract, has been considered a very difficult procedure Besides this difficulty, even if the anastomosis is successfully carried out, the lack of a sphincter muscle will result in urinary incontinence

For these reasons, we hesitated to carry out these surgical procedures But the artificial external urinary fistula is inconvenient considering the social life of patients In this report we describe a case on which a new operative method was performed, which is called by us antepubic vesico-ileal-neourethrostomy, for defects of the posterior urethra and the neck of the urinary bladder Using this operation we could almost attain our goal

CASE REPORT

A 60-year-old man, Japanese, had previously had rectal resection for cancer of the rectum On March 8, 1955 an artificial anus had been built as a primary procedure On March 15, 1955 a radical operation for the cancer had been done by the abdominoperineal method The carcinomatous infiltrations involved the posterior urethra, prostate gland, seminal vesicles and the neck of the urinary bladder So these organs were removed together with the rectum (fig 1) The defect in the neck of the urinary bladder was closed and an external urinary fistula placed on the abdomen

The postoperative course was favorable, but the external urinary fistula was so uncomfortable for the patient's life that he earnestly wished to urinate in the natural way Therefore, the newly devised operation just mentioned was performed

On April 16, 1955 the abdomen was opened by a 15 cm paramedian section on the right side Adhesions were found here and there caused by the previous laparotomy Various parts of the ileum were pulled up with the fingers and were tested to find a part with a mesentery long enough to bring the part near the scrotum

A 20 cm long segment of ileum which was most suitable for this purpose was cut off from the intestinal tract keeping the blood supply The segment of ileum

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Finally the artificial urinary fistula was operatively closed and the antepubic vesico-ileal-neourethrostomy was completed (fig 4, *C*)

We succeeded in keeping urine in the urinary bladder by means of a belt with a rubber balloon over the pubis (fig 4, *A* and *B*) The belt and balloon compensated for the external sphincter of the urinary bladder The patient, wearing the pressing belt, could take a walk without using a pouch to collect urine from the external urethral orifice He could voluntarily void through the natural urinary path by unfastening the belt (fig 5)

DISCUSSION

Various methods are available for treating defects of the posterior urethra and neck of the bladder But as the reconstruction of a urethra is considered difficult, many workers are inclined to put the destroyed portion out of the urinary circuit by making an external fistula or performing Coffey's ureterocolostomy

Thanks to the recent advance in the study of antibiotics, a urinary pathway has been made by several surgeons using a segment of intestine For instance, the cecum has been used for defects of the urinary bladder Barnes in particular devised an interesting method for the anastomosis of the bladder and urethra by making a flap with a part of the bladder wall His mode of operation was not only complicated but failed in the restoration of function both in voluntary urination and in the storing of urine in the bladder

Our method almost fulfilled the principle that urine must be excreted through the urethra and at the same time voluntary urination should be possible We have found no report similar to ours

The success of the anastomosis between urethra and intestine will widen the possibility of radical operation for cancer of the rectum, because this offers a solution to the problem of the defect of the urinary tract and the sphincter muscles

However, our mode of operation is not yet a complete one The patient can hold his urine while he is standing without incontinence, but during postural changes, such as from standing to sitting down, urine sometimes leaks through the urethral orifice because of momentary relaxation of the belt

There are a few other problems to be improved or discussed in our method for instance, preventing the insufficient suture of anastomosis

Concerning this problem, our experience taught us that making a preliminary artificial urinary fistula in the interposed segment of intestine until the complete recovery of the anastomosis will give much better results than placing a catheter in the urinary tract following the operation

It has not been determined in which direction anastomosis should be done, antiperistaltically or isoperistaltically Hinman and Belt, Baird, Scott and Spencer, Bollman and Mann studied the physiology after transplantation of intestine in the urinary tract and described the harmful resorption of urine through the transplanted intestine and the accumulation of nonprotein nitrogen, CO and Cl-ion in the blood Matsumoto and Merscheimer, MacLean and Fais claim, however, that the resorption through the transplanted intestine is only a transitory phenomenon for a week following the operation

There is the problem of ascending infection in the application of intestine for the reconstruction of the urinary tract Our patient had only slight symptoms of cystitis after operation which responded in a week to the use of antibiotics

Now, he has been quite healthy for 12 months following the rectal amputation without any sign of recurrence of carcinoma

CONCLUSION

A new operation was successfully performed on a patient who was suffering from incontinence of urine after radical operation for cancer of the rectum The method of operation was called by us antepubic vesico-ileal-neourethrostomy Our method fulfilled to some extent the goal of restoration of voluntary urination

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THE PROBLEMS OF CORD BLADDER REHABILITATION

A ESTIN COMARR

From the Paraplegia Service of the Veterans Administration Hospital, Long Beach, Calif and the Department of Urology, School of Medicine, College of Medical Evangelists, Los Angeles, Calif

There are authors who feel that a patient with a spinal cord injury, if adequately treated, will infallibly develop an automatic bladder[1] [2] This expectation does not hold Among other reports it has been shown that of 844 patients at this Paraplegia Center, 76 per cent had no catheters, whereas 24 per cent had catheters[3] The problems of the neurophysiology and treatment of neurogenic bladders have been fully reviewed in the recent literature[3] [6]

The purpose of this paper is to examine the situation among our hospitalized patients in order to ascertain 1) how many patients became catheter-free on straight drainage, 2) how many patients became catheter-free on tidal drainage and/or bladder training, 3) how many patients became catheter-free by other methods, 4) how many patients have never been catheter-free and its cause, 5) how many patients have regressed so as to need catheters and the cause of the regression

One hundred eighty hospitalized patients and a few outpatients at random were interviewed Patients injured less than six months were not included in this study

RESULTS

Thirty-four patients became catheter-free while on straight drainage The majority of them were transferred from other institutions where tidal drainage and/or bladder training were not practiced Irrespective of the level or completeness of the lesion all but one patient became catheter-free within six months

Five patients had catheters for periods ranging from 9 months to 3 years The patients had been on straight drainage until a physician suggested that a residual test be performed and a balanced bladder function was found The time since injury ranged from 1½ to 40 years, and the patients still are catheter-free

Twenty-seven patients became catheter-free while on tidal drainage and/or bladder training All but two became catheter-free within six months irrespective of level or completness of injury The duration of tidal drainage and/or bladder training varied from 1 to 32 weeks Five of the 27 patients had been on bladder

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[2] Munro, Donald Injuries to Nervous System Philadelphia W B Saunders Co , 1952

[3] Bors Ernest Bladder disturbances and management of patients with injury to spinal cord J Internat Coll Surg , **21** 513–527, 1954

[4] Bors, Ernest Veterans Administration Technical Bulletin TB 10-503 Washington 25, D C Dec 18, 1948

[5] Bors, Ernest Role of anatomy and physiology for understanding of neurogenic bladder To be published, J Indian Med Profession, Bombay India

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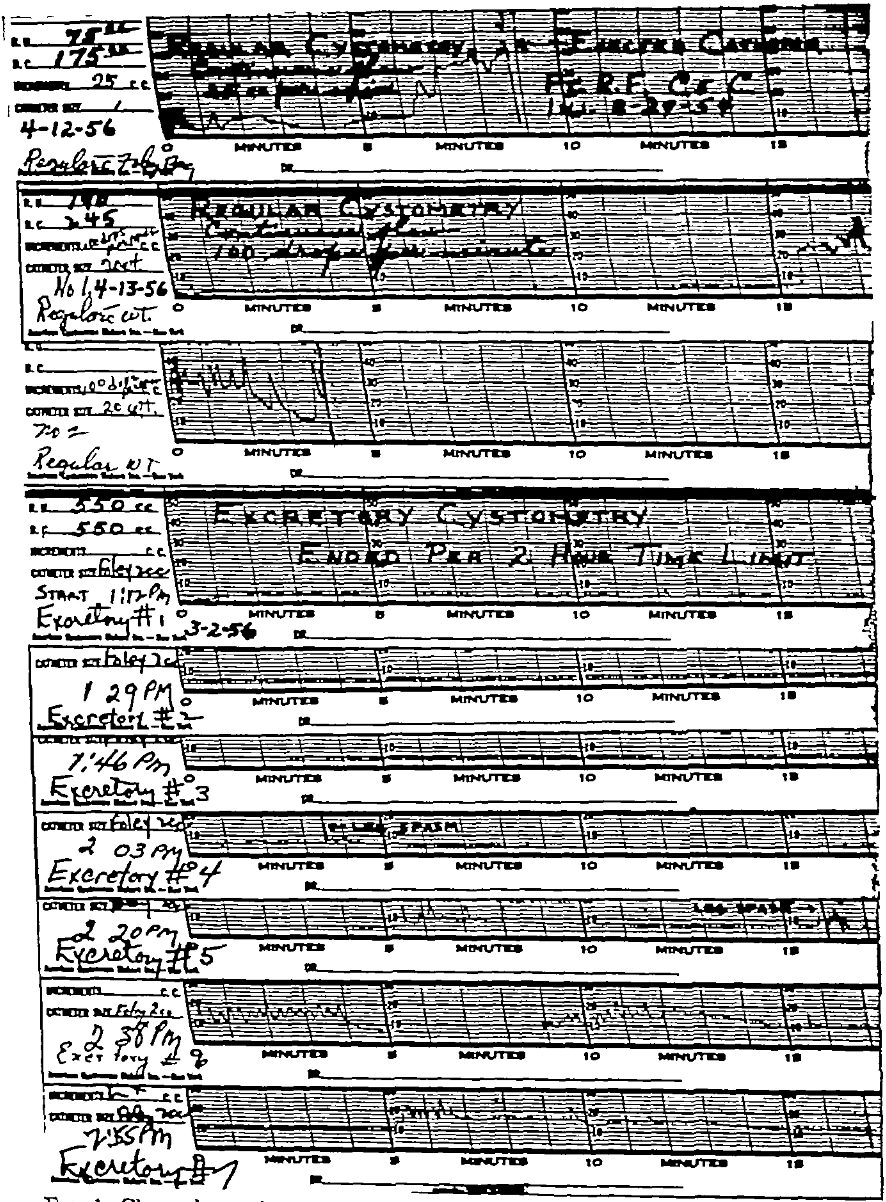

FIG 1 Chart shows that excretory cystometry is more physiologic It was performed on patient injured 8-29-54 who sustained a C 5 clinically complete lesion Note that regular cystometry performed at increments of 25 cc per minute (continuous flow) revealed only 175 cc capacity Regular cystometry at 100 drops per minute (continuous flow) revealed 245 cc capacity Yet, excretory cystometry revealed capacity of 550 cc

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Nineteen patients became catheter-free by other procedures The majority of these cases had been on tidal drainage and/or bladder training prior to the pro-

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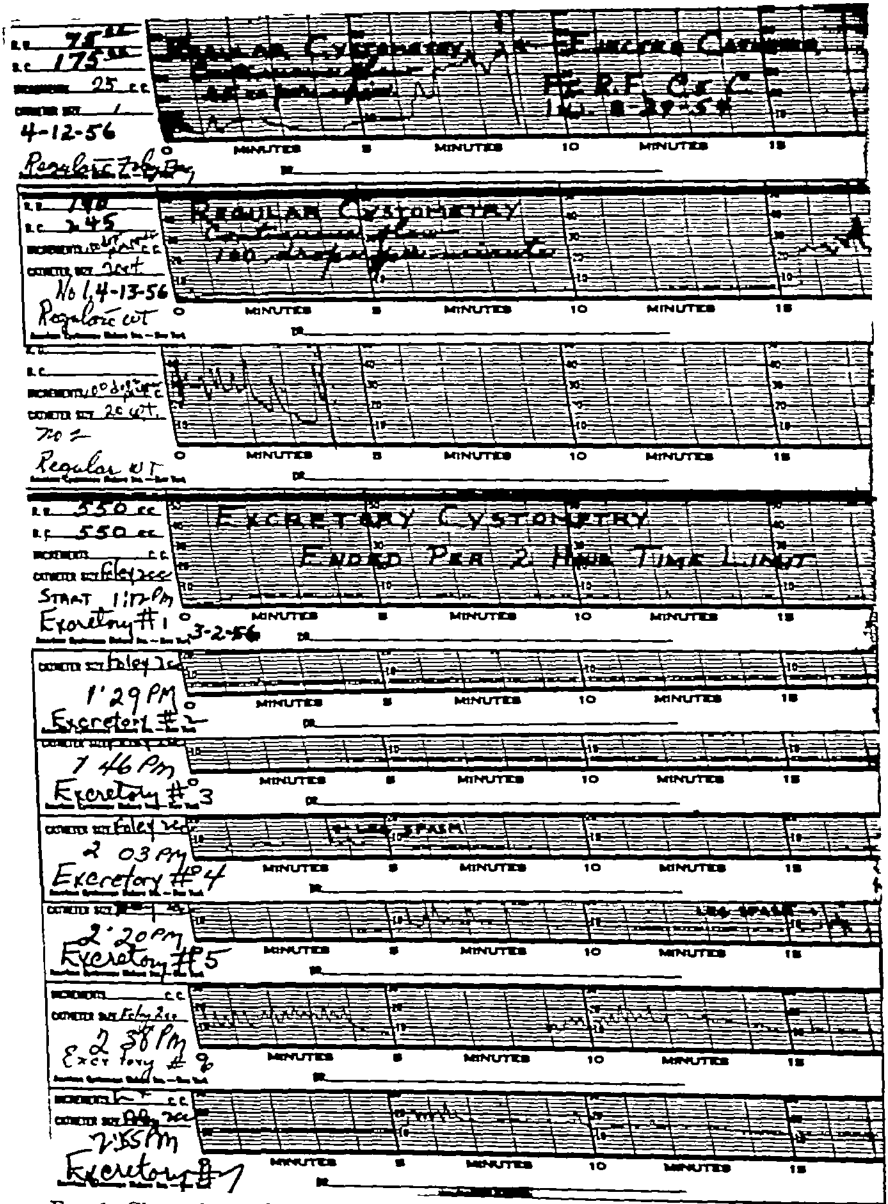

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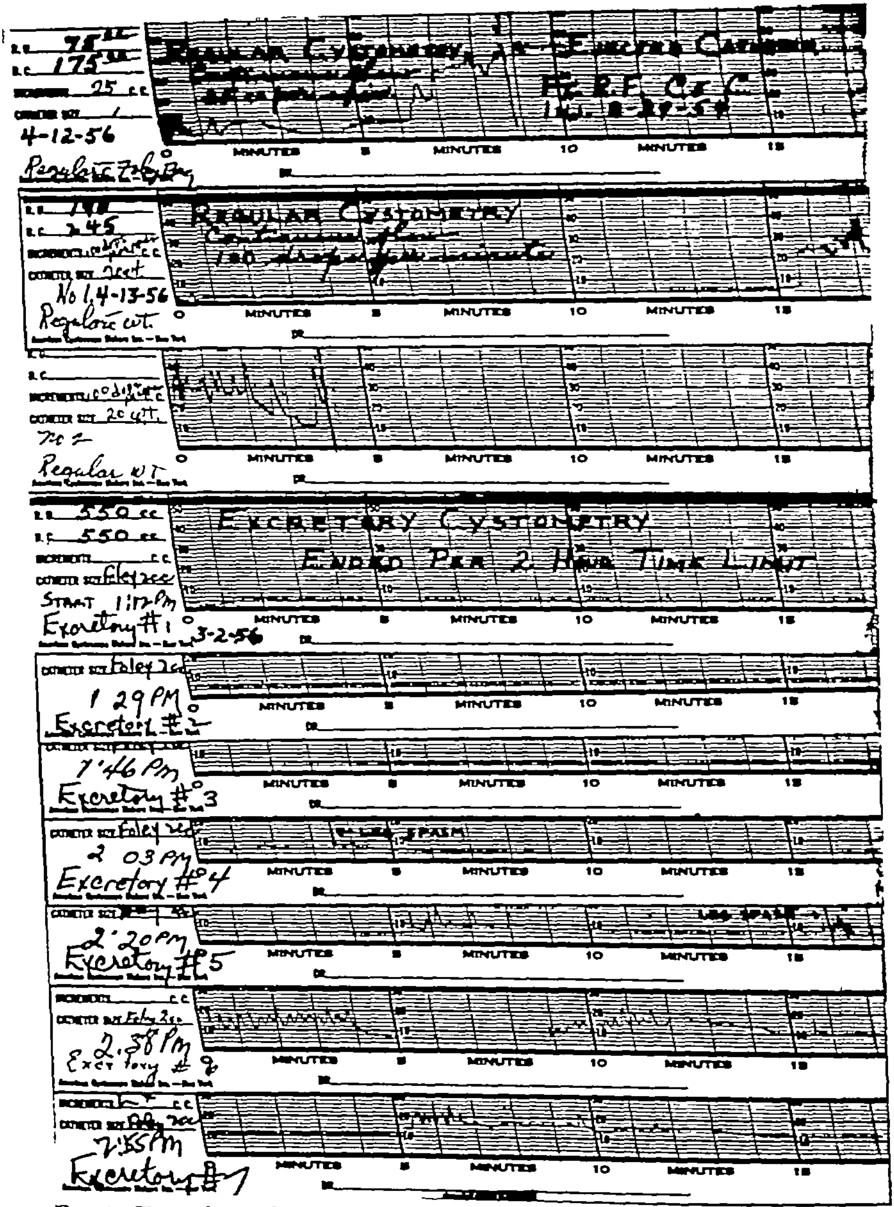

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cedures that made them catheter-free The time which passed until they became catheter-free ranged from 12 weeks to 3½ years

Sixty-two patients have never been catheter-free Yet, they have been under our care from 2 months to 11 years Forty-seven (75 per cent) of these patients have cervical lesions The remaining 15 (25 per cent) have injuries at other levels

The reasons which necessitated uninterrupted catheter drainage in 62 patients were inability to credé or strain, paroxysmal hypertension, renal calculosis, persistent low grade fever, un-cooperative patients, patient preference, vesicoureteral reflux, penoscrotal fistulas and inability to create automaticity

The bladder function of 33 patients regressed to such a degree that catheters were needed after varying periods of having been catheter-free

DISCUSSION

After a review of the statistics one cannot agree entirely with Munro's statement that, "tidal drainage, cystometry and bladder training are interdependent When properly used in combination they insure that every patient who has had an injury to the spinal cord, conus or cauda equina, and who is intelligent and co-operative, will have infallible 24 hour control of urination regardless of the severity of the cord injury "[1]

One hundred and eighteen (66 per cent) patients are or have been catheter-free if we include the group of patients with regression of bladder function

Thirty-nine patients became catheter-free while on straight drainage Fourteen patients of the group with regression of function became catheter-free originally on straight drainage Therefore, 53 (45 per cent) of the 118 patients became catheter-free while on straight drainage

Twenty-seven patients became catheter-free by tidal drainage and/or bladder training Four patients of the group with regression of function became catheter-free originally while on tidal drainage and/or bladder training Therefore, 31 (26 per cent) of 118 patients became catheter-free while on tidal drainage and/or bladder training

Nineteen patients became catheter-free by other methods (transurethral vesical neck resection, pudendal blocks, pudendal operations, obturator neurotomies and adductor myotomies, topical mucosal anesthesia of bladder with pontocaine, ice water stimulation of bladder) Fifteen patients of the group with regression of function became catheter-free by other methods (pudendal blocks, transurethral vesical neck resection, subarachnoid alcohol block) Therefore, 34 (29 per cent) of 118 patients became catheter-free by other methods It should be noted that the majority in this group had been on tidal drainage and/or bladder training before other procedures had to be instituted

Eighty-seven (74 per cent) of 118 patients became catheter-free without tidal drainage and/or bladder training as the contributing factor

The question arises Would the bladder function of those patients whose "catheter-free state" is attributed to tidal drainage and/or bladder training have returned, had they not been on that regimen? This is difficult to answer since it is accepted practice to place patients with a spinal cord injury on tidal drainage and/or bladder training. In spite of the interesting findings brought out by this study, tidal drainage and/or bladder training is still good treatment if considered in the following order: 1) rehabilitation of the viscus, 2) prevention of bladder contracture, 3) psychological reasons.

Rehabilitation of the viscus by means of tidal drainage and/or bladder training should be considered as another aid in the treatment of the neurogenic bladder, despite the fact that our study has shown that it is not the panacea claimed by others. We agree that it aids in "conditioning the reflex",[1] but it is not infallible. Tidal drainage is a good method of cleansing the bladder and thereby diminishes infection, yet, it does not necessarily prevent formation of calculi in the bladder. Recent studies with "excretory cystometry" showed that upon drinking one glass of water (240 cc) hourly beginning at 7:00 a.m., the output in a 1½ hour period varied markedly.[7] In one patient 990 cc was collected in a 1½ hour period. A similar observation was made by Munro in a later publication wherein he suggested that the intake of fluid be decreased beforehand where expected peaks of output are found.[2] However, it has been shown that adequate amounts of fluid are important for prevention of renal calculi.[8] It is, therefore, suggested that bladder training be done by allowing one glass (240 cc) of water hourly beginning at 6:00 a.m. until bed time. The bladder should be emptied periodically as indicated by previous testing. Our experience contraindicates the use of 300 cc of water hourly, and the eventual 3-hour clamping off period, as proposed in the literature,[1] and is considered by us to be much too long.

Tidal drainage and/or bladder training may play a role in the prevention of bladder contracture as shown by the following observations. Four patients with an upper motor neuron type of bladder[3, 5] who had been on straight drainage from 2½ to 6 years had bladder capacities which varied from 90–100 cc. *Per contra*, one patient who, as the great exception, continued with his training, retained a capacity of 250 cc. He has a lesion at C-7, clinically complete, which resulted from injury 8 years ago. During the day he clamps off his catheter until he develops a chilly sensation (cutis anserina) which is a pathologic autonomic reflex.[4] This patient, too, is an example of the value of bladder training in preventing bladder contracture.

Five other patients who had been on straight drainage from 3 to 9 years had capacity studies performed. They had had subarachnoid alcohol blocks or anterior rhizotomies with a subsequent lower motor neuron type of bladder.[4] Yet, their bladder capacities varied from 235–400 cc, i.e., no contracture had developed. It may be added parenthetically that bladder contracture has not become a problem of such magnitude at this center as to require or even to consider cutaneous ureterostomy. We believe that every patient with a spinal cord injury has probably a bladder with its own "inherent physiologic capacity," which we can only endeavor to maintain.

On questioning those patients whose bladders started to function while on bladder training, the "catheter-free state" was enthusiastically attributed to this regimen What these patients did not know was that 74 per cent of their fellow patients could not attribute their success to bladder training The psychological value of tidal drainage and/or bladder training is, therefore, obvious The patient feels that he is being actively treated during the first 6 months of conservative care By adhering to this regimen, religiously clamping and unclamping the catheter, the patient is motivated toward a desirable goal which is worth his while and effort

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As noted previously, 53 patients became catheter-free while on straight drainage Fifty-two of the 53 patients did so in periods varying from a minimum of hours or days after injury to a maximum of 6 months after injury This, then, would indicate that conservative (non-intervention) therapy should extend at least up to six months after injury, thereafter, therapy with intervention of some type should follow as indicated in the individual case

A conservative estimate indicates that 50 of the 62 patients who have never been catheter-free will remain permanently on catheter drainage The great majority of these are tetraplegics [6] Permanent drainage will also be necessary in about 25 of the 33 patients whose bladders regressed Therefore, 75 (42 per cent) of the 180 interviewed patients will probably need permanent catheters

The term "regression" of bladder function is probably used too loosely Actual regression, i e , spontaneous imbalance of function without a detectable cause, was found in only 5 patients whereas the remaining 28 patients needed the re-establishment of catheter drainage because of various complications (vesicoureteral reflux, penoscrotal fistulas and diverticula, urethroischial diverticula, hydronephrosis, renal calculi, pyelonephritis, vesical neck stricture, chordotomy)

Experience at this center has shown that patients who had catheters for many years have clinically faired very well in regard to kidney function This should, by no means, infer that we should not continue in every possible way to create a "catheter-free state," because of the many other complications which accompany a life with a permanent catheter, such as urethral changes at the penoscrotal junction, and/or epididymitis The neurogenic bladder will remain a challenge to the urologist, because its function cannot be predicted with certainty

SUMMARY

Of 180 patients interviewed at the Veterans Administration Paraplegia Center at Long Beach, 85 (47 per cent) are catheter-free Ninety-five (53 per cent) patients have catheters, 62 have never been without catheters and 33 regressed so as to need reintroduction of catheters

Of the 180 patients, 118 (66 per cent) were catheter-free at one time or another whereas 62 (34 per cent) have never been catheter-free Of the 118 patients, 53 (45 per cent) became catheter-free by straight drainage, 31 (26 per cent) by tidal drainage and/or bladder training, 34 (29 per cent) by other methods

It is concluded that tidal drainage and/or bladder training is not a panacea However, it should remain the accepted practice for the following reasons 1) rehabilitation of the viscus, 2) possible prevention of bladder contracture, and 3) psychological reasons

It was again shown that surgical intervention for a ' catheter-free state ' should not be instituted until a minimum of six months has elapsed since injury

Briefly, a modification for bladder training has been suggested

Addendum The results of Excretory Cystometry—A More Physiologic Method" mentioned in this paper will appear in another publication See figure 1

The technique briefly, is as follows The patient is awakened at 6 00 a.m and started on 1 glass of water every hour per os until his scheduled time for cystometry The glass of water on the hour is continued even during cystometry A catheter (No 20) is introduced into the urethra slowly and gently until urine presents itself and the bladder is emptied Strain, credé or any other method is not used to empty the bladder since this might set off reflex activity The tip of the catheter should be past the vesical neck The catheter is then connected to the Lewis cystometer in the usual manner except that fluid is not introduced into the bladder retrogradely The intravesical volume is the urine which is excreted during the examination Sufficient time should be allowed for stabilization before the investigation is started in order to avoid recording of responses which are due to change of catheters, moving of the patient to the testing room, moving the patient from guerney to cystoscopy table and the like (It is best to perform the procedure in the patient's bed)

The cystometer is permitted to run until the catheter is ejected Yet it is not permitted to run more than 1½ to 2 hours bladder training, the "catheter-free state" was enthusiastically attributed to this regimen What these patients did not know was that 74 per cent of their fellow patients could not attribute their success to bladder training The psychological value of tidal drainage and/or bladder training is, therefore, obvious The patient feels that he is being actively treated during the first 6 months of conservative care By adhering to this regimen, religiously clamping and unclamping the catheter, the patient is motivated toward a desirable goal which is worth his while and effort

As noted previously, 53 patients became catheter-free while on straight drainage Fifty-two of the 53 patients did so in periods varying from a minimum of hours or days after injury to a maximum of 6 months after injury This, then, would indicate that conservative (non-intervention) therapy should extend at least up to six months after injury, thereafter, therapy with intervention of some type should follow as indicated in the individual case

A conservative estimate indicates that 50 of the 62 patients who have never been catheter-free will remain permanently on catheter drainage The great majority of these are tetraplegics[6] Permanent drainage will also be necessary in about 25 of the 33 patients whose bladders regressed Therefore, 75 (42 per cent) of the 180 interviewed patients will probably need permanent catheters

The term "regression" of bladder function is probably used too loosely Actual regression, i e , spontaneous imbalance of function without a detectable cause, was found in only 5 patients whereas the remaining 28 patients needed the reestablishment of catheter drainage because of various complications (vesicoureteral reflux, penoscrotal fistulas and diverticula, urethroischial diverticula, hydronephrosis, renal calculi, pyelonephritis, vesical neck stricture, chordotomy)

Experience at this center has shown that patients who had catheters for many years have clinically faired very well in regard to kidney function This should, by no means, infer that we should not continue in every possible way to create a "catheter-free state," because of the many other complications which accompany a life with a permanent catheter, such as urethral changes at the penoscrotal junction, and/or epididymitis The neurogenic bladder will remain a challenge to the urologist, because its function cannot be predicted with certainty

SUMMARY

Of 180 patients interviewed at the Veterans Administration Paraplegia Center at Long Beach, 85 (47 per cent) are catheter-free Ninety-five (53 per cent) patients have catheters, 62 have never been without catheters and 33 regressed so as to need reintroduction of catheters

Of the 180 patients, 118 (66 per cent) were catheter-free at one time or another whereas 62 (34 per cent) have never been catheter-free Of the 118 patients, 53 (45 per cent) became catheter-free by straight drainage, 31 (26 per cent) by tidal drainage and/or bladder training, 34 (29 per cent) by other methods

It is concluded that tidal drainage and/or bladder training is not a panacea However, it should remain the accepted practice for the following reasons 1) rehabilitation of the viscus, 2) possible prevention of bladder contracture, and 3) psychological reasons

It was again shown that surgical intervention for a 'catheter-free state' should not be instituted until a minimum of six months has elapsed since injury

Briefly a modification for bladder training has been suggested

Addendum The results of "Excretory Cystometry—A More Physiologic Method" mentioned in this paper will appear in another publication See figure 1

The technique, briefly, is as follows The patient is awakened at 6 00 a.m and started on 1 glass of water every hour per os until his scheduled time for cystometry The glass of water on the hour is continued even during cystometry A catheter (No 20) is introduced into the urethra slowly and gently until urine presents itself and the bladder is emptied Strain credé or any other method is not used to empty the bladder since this might set off reflex activity The tip of the catheter should be past the vesical neck The catheter is then connected to the Lewis cystometer in the usual manner except that fluid is not introduced into the bladder retrogradely The intravesical volume is the urine which is excreted during the examination Sufficient time should be allowed for stabilization before the investigation is started in order to avoid recording of responses which are due to change of catheters moving of the patient to the testing room, moving the patient from guerney to cystoscopy table and the like (It is best to perform the procedure in the patient's bed)

The cystometer is permitted to run until the catheter is ejected Yet, it is not permitted to run more than 1½ to 2 hours

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INFLUENCE OF HYPOPHYSECTOMY AND REPLACEMENT THERAPY ON EXPERIMENTALLY INDUCED CALCULI IN RATS

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Dunning, Curtis and Madsen,[1] in 1951, reported a sex incidence favoring males in diethylstilbestrol-induced bladder calculi In 1955, Marshall and co-workers[2] reported that experimental cystolithiasis in Wistar rats had a marked sex incidence favoring the male We have found that in female Long-Evans rats the low incidence and small size of experimentally induced bladder stones could be increased to the high male incidence and size by ovariectomy and testosterone treatment [3] These experiments clearly implicate the androgens as a contributing factor in calculus formation and growth

The present study was conducted in an attempt to discover of what importance the stimulating effects of pituitary hormones were on calculus formation and growth

MATERIALS AND METHODS

Cylindrical, c p magnesium ribbon niduses were aseptically introduced into the bladders of Long-Evans and Sprague-Dawley rats, some of which had previously been hypophysectomized Vermeulen's[4] technique was employed for the implantation The animals were fed Purina Laboratory Chow and water *ad libitum* Each group consisted of 20 animals Intramuscular injections were begun the first postoperative day

The control animals received 0 1 ml of 1 per cent gum acacia daily The following doses of hormones were used

ACTH (Armour)	0 5 mg daily
Gonadotrophins	
APL (Ayerst)	4 i u daily
Equinex (Ayerst)	4 i u daily
Luteotrophin (Squibb)	10 i u daily
Testosterone cyclopentyl propionate (Upjohn)	10 mg per week
Growth hormone (Armour)	0 05 mg daily

Twenty-four hour urine volumes were determined for each animal

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TABLE 1 *Stones formed in Sprague-Dawley rats 6 weeks after implantation of magnesium nidus*

Endocrine Condition	No of Animals	Incidence of Calculi	Average Weight*
		per cent	*mgm*
Normal male	19	100	83 4
Normal female	16	100	51 6
Hypophysectomized males	13	7	†
Hypophysectomized males, ACTH	8	50	10 6
Hypophysectomized males, gonadotrophins, 4 i u of each	12	75	21 8
Hypophysectomized males, ACTH plus gonadotrophins	7	100	35 3

* Includes weight of nidus

† Only one calculus weighing 13 mg in group

In the experiments shown in table 2, there were five additional animals in each treatment group These animals had no magnesium nidus and were used to collect urine specimens for determination of calcium, magnesium and phosphorus Calcium was determined by Denis' method,[5] magnesium, according to Terri,[6] and phosphorus, as phosphate, after Fiske and Subbarow [7]

All animals were sacrificed 6 weeks from the time of implantation of the nidus, except the hypophysectomized animals in table 2, which were sacrificed at 4 weeks The urinary pH was determined by test paper All animals showing urinary pH greater than 7 0 were discarded Calculi were removed, blotted and weighed immediately Gram stains were made of the urinary sediment Statistical correlations were made by Fisher's method and the probability determined from his table [8]

RESULTS

Tables 1 and 2 show that there was a less marked difference in sex incidence of calculi in Sprague-Dawley rats than in the Long-Evans strain However, even though there was a high incidence of calculus formation in Sprague-Dawley females, their significantly smaller size, p less than 01, indicates the trend seen more dramatically in the Long-Evans strain

Hypophysectomy in both strains reduced stone formation to practically nil In each experiment, only one rat had a stone, and these were only 3 and 4 7 mg of crystals, respectively

When adrenal stimulation was induced, half of the treated animals developed a few crystals on the nidus Administration of gonadotrophins gave a 75 per cent incidence of calculi, averaging 25 mg Simultaneous treatment with ACTH and

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TABLE 2 *Stones formed in Long-Evans rats 4 weeks after implantation of magnesium nidus*

Endocrine Condition	No of Animals	Incidence of Calculi	Average Weight*
		per cent	*mgm*
Normal males*	19	100	182
Normal females*	20	54	24
Hypophysectomized males	11	9	†
Hypophysectomized males, luteotrophin	11	27	24 6
Hypophysectomized males, growth hormone	17	76	46 1
Hypophysectomized males, testosterone	13	92	81 5

* Calculi formed during 6 weeks period

† One rat had a calculus weighing 14 7 mg

TABLE 3 *Total 24 hour urinary calcium, magnesium and phosphorus excretion in hypophysectomized rats, average values for 15 samples in milligrams per 24 hours*

Treatment	Calcium	Magnesium	Phosphorus
Intact control males	0 14	0 93	13 2
Intact control females	0 19	1 00	6 9
None	0 13	0 13	4 2
ACTH	0 09	0 04	6 0
Gonadotrophins	0 52	0 17	6 4
ACTH + gonadotrophins	0 35	0 49	6 8
Luteotropin	0 12	0 30	6 1
Growth hormone	0 04	0 16	8 7
Testosterone	0 09	0 29	5 9

gonadotrophins increased the incidence to 100 per cent, and size to 35 mg Luteotrophin produced only a few small stones Growth hormone treatment gave stones of larger size

The best stones produced were those obtained by testosterone treatment These stones were 45 per cent of the size obtained in normal male animals of the same strain Statistical probability in the above groups was less than 1 per cent that the results were due to chance Although urine volumes varied from day to day and rat to rat, no consistent or significant variations were related to treatment Infection was not found to be an important contributing factor in those animals whose urinary pH was less than 7 0

The results of urinary calcium, magnesium and phosphorus studies are compiled in table 3 Urinary calcium excretion was considerably reduced by growth hormone Calcium excretion was markedly increased by gonadotrophins Magnesium excretion was markedly increased by luteotrophin and combined treatment with ACTH and gonadotrophins ACTH significantly reduced magnesium and calcium excretion Phosphorus excretion was increased by growth hormone, and reduced by testosterone treatment

Table 4 gives the average weights of the whole prostates of each treatment group

TABLE 4 *Average prostate and testis weight in hypophysectomized animals subject to several treatments*

Treatment	Prostate Weight	Testis Weight
	grams	*grams*
None	0 034	0 209
Gonadotrophins	1 402	2 286
Gonadotropins + ACTH	1 483	2 235
Testosterone	1 113	0 766
Luteotrophin	0 068	0 411
Growth hormone	0 145	0 734

DISCUSSION

The difference in sex incidence and size of calculi in the two strains of rats used suggests that the Wistar strain is the genetic origin of this marked sex difference This is borne out by Vermeulen's studies in Hoffman albino rats, our studies in Sprague-Dawley albinos and those of Marshall's group The Long-Evans strain is a hybrid between the Wistar and a wild strain Although the tendency is not marked in albino rats, it can be disclosed by using large groups and by endocrine manipulations The sex difference in Dunning, Curtis and Madsen's chronically estrogenized rats was probably the result of squamous metaplasia in the lower urinary tract

Hypophysectomy reduced calculogenesis to practically nil The apparent mechanisms involved are only partly answered by the present experiments Lactogenic hormone, or luteotrophin, which has been found to be important to prostate growth, and which doubled the size of the prostates in our hypophysectomized rats, had no important effect on calculus formation ACTH is similarly not important when given alone Treatment of hypophysectomized animals with growth hormone, gonadotrophins, gonadotrophins and ACTH or testosterone increased the incidence and size of calculi The mechanisms probably differ in the several groups Judging from urinary excretion studies of calcium, magnesium and phosphorus, the important change induced by growth hormone is the increased urinary phosphate excretion Hyperphosphaturia in presence of normal levels of magnesium would increase the solubility product and lead to more rapid deposition of magnesium phosphate This mechanism in the above experiments was peculiar to growth hormone treated animals Gonadotrophin treatment increased urinary calcium to levels averaging five times normal When ACTH was also given, magnesium excretion was increased With unchanged urine volumes, the hypercalciuria and hypermagnesuria could be expected to produce more and larger calculi Mechanisms for testosterone and luteotrophin calculus stimulation apparently are similar insofar as hypermagnesuria is involved But this mechanism is clearly not sufficient to explain the marked difference between these two groups The mechanisms whereby testosterone stimulates calculus formation are not clarified by the present study There are probably factors other than the urinary electrolytes which are responsible

If the weight of the prostate were a reliable index of androgen status, then the gonadotrophin, ACTH and gonadotrophin groups should have formed the best stones Table 4 shows that, even though the testosterone treated group had less well developed prostates, the stones were larger The increased size of prostates in rats treated with growth hormone could be due to gonadotrophin impurities in the preparation However, the urinary excretion of calcium and magnesium does not confirm this theory

SUMMARY AND CONCLUSIONS

Hypophysectomy virtually abolishes the tendency to calculus formation about a magnesium nidus in both high and low incidence calculus strains of rats

The administration of testosterone to hypophysectomized rats restores the tendency to calculus formation, partly by increasing urinary excretion of magnesium, and by unknown factors

Administration of gonadotrophins and combined gonadotrophins and ACTH increases the incidence and size of experimental calculi, but less effectively than does testosterone The mechanism is, probably, increased calcium and magnesium excretion

Growth hormone is even less effective, ACTH and luteotrophin were ineffective

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DIVERTICULUM OF THE FEMALE URETHRA A NEW METHOD OF ABLATION

MILO ELLIK

As more routine examinations include a search for diverticulum of the female urethra, the number found rises This increased awareness proves that such outpouchings are not a too infrequent problem A large single series of cases seems unlikely as the Cleveland Clinic reported only 7 in a period of 22 years (then added 38 more between 1943 and 1954) The Mayo Foundation recorded a mere 71 cases prior to 1949 and only 30 were seen at Johns Hopkins between 1890 and 1949 Pathogenesis of these cul de sacs remains controversial, but clinically they present a fairly standard pattern They are usually palpable and sometimes visible along the roof of the vagina, the contents may be expressible or not, the urethral ostium may be patent or closed and located either inside or distal to the external sphincter The fluid content may be infected and, of course, they may produce a variety of symptoms Usually concealed and closely enveloped by the vaginal vault a diverticulum may be difficult to see as well as hard to mobilize When the urethral stoma is sealed it is difficult to find endoscopically, when it is open the escape of fluid content detracts from the turgid outline of the mass Should the urethral opening be close to the bladder neck the portent of postsurgical urethrovaginal fistula spells catastrophe If the sac is multiloculated, has multiple stomata, contains stone, tumor or embraces an ectopic ureteral orifice, the problem is compounded Therefore, preoperative study had best be thorough and treatment guided with meticulous caution Surgical ablation is the usual treatment but may be accompanied by qualms, tedium and hazard on the part of the operator The most simple, small, turgid, uninfected and distally located diverticulum can be a delicate operative problem

When Moore, in 1950, described his balloon catheter technique he undoubtedly did so because he felt that it aided in an otherwise difficult, irksome and precarious operation His technique was widely used and accepted In spite of this advance, however, sharp surgical dissection remained troublesome The sac was often thin, fragile and became disrupted before the dissection was completed In such instances the residual pouch with its urethral ostium was lost in a bloody quagmire Understandable concern hovered over the eventual outcome If the operator knew the urethral opening communicated between the sphincter and bladder neck he was apt to defer the case or suggest digital evacuation as an alternative Such patients were vexed and continued to have their symptoms and periodic infections

Early in 1953 this author was confronted at surgery by a diverticulum with a patent opening communicating distal to the sphincter An extension of this sac was found to migrate far back under the trigone and the contents were foul Surgical excision might have been simple enough had it not been for the sub-

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Read at annual meeting of Western Section of American Urological Association, San Francisco, Calif April 30–May 3 1956 trigonal ramification Because of this it was decided to omit formal dissection, to merely cleanse the entire cavity and pack it with gauze Conventional gauze did not appeal, so oxycel was used The excellent result encouraged a thought that all of these cavities might be similarly treated, and if so, such an obvious simplification could be most welcome and rewarding This report is prompted by a small series of similar experiences

REVIEW OF CASES

Seven cases comprise this series, the first patient having been operated upon in 1953 All diverticula were palpable, visible, or both Two actually protruded from the introitus sufficiently to be apparent to the patient as well as the physician Four had open urethral orifices and could be digitally evacuated Three could not be emptied as their openings were temporarily sealed, and their contents odorless, clear and sterile It was shown that of the four expressible sacs, three opened outside the sphincter and one close to the bladder The three turgid, unexpressible diverticula were so close to the bladder neck that it was assumed their sealed stomas were cephalad to the sphincter, when urethroscopic proof was not available Preoperative study included complete cystoscopy and retrograde pyelography, along with urethroscopic appraisal Urethrography was not utilized, but may be in the future, and is to be recommended Two had ramifications, both being in the direction of the trigone One of these was never completely explored or outlined and it is not known just how far or in what direction it eventually progressed All were subjected to the same treatment and the results were uniformly satisfactory After 2 weeks postoperatively healing and resolution had erased all evidence of the mass, the patients appeared to have been relieved of their symptoms and only the healed surgical scar could be seen or palpated Subsequent urethral calibrations and dilatations were done, but no strictures were noted

AUTHOR'S TECHNIQUE

The position of the patient is either that of lithotomy or prone genuflection (as favored for hemorrhoidectomy) The latter is preferred as it presents the lesion in a convenient dorsal position Usually an inlying Foley urethral catheter provides traction and delineation The diverticulum is visualized and palpated or if collapsed, its position demonstrated by some small, hooked director placed through the urethral ostium The hooked director should be small enough not to overstretch the urethral stoma and may be either a curved forceps, a malleable probe or even a ureteral catheter The outermost aspect of the presenting mass is grasped by two Allis forceps and a short stab incision made, between them, directly into the diverticulum Following drainage of the cavity the forceps are reinserted to include sac lining The cavity is then flushed thoroughly with hydrogen peroxide, or the operator's choice of similar irrigation The inner lining may be excoriated with a tiny bit of plain gauze, such as the so-called "peanut" gauze sponge, held in the tip of a mosquito forceps No attempt is made to close the ostium (although in certain instances suturing might be considered proper and useful) The cleansed and abraided cavity is then stuffed with oxycel strips These strips are usually about one-fourth inch wide or slightly wider, and the number of strips used contingent upon the size of the diverticulum Although the sac need not be tightly filled, it should be palpable as a semi-solid mass after sufficient oxycel has been inserted Gelfoam might be substituted for oxycel, but was not used in this series The smallness of the stab wound aids in the retention of the oxycel gauze, the incision is then closed with an appropriate number of interrupted chromic sutures No drains are used and a vaginal pack is optional The Foley urethral catheter is allowed to remain indwelling for a period of two to seven days postoperatively, depending on the size of the urethral stoma or the whim of the operator If no urethral communication exists the indwelling catheter might be removed at once This type of technique has been used without regard for size of sac or urethral ostium, the presence of infection, the existence of ramification or whether the urethral opening presented on the bladder or the meatal side of the sphincter It is conceivable, however, that in a very large and redundant mass some of the excess might be profitably excised The presence of new growth, stone or ectopic ureteral orifice within the cavity could be a rare and extenuating circumstance

COMMENT

Packing these cavities with conventional gauze was described and discarded long ago Cabot, in an early text, stated that this often required secondary closure, particularly of the fistula that sometimes followed The recent advent of absorbable gauze, in addition to being welcomed in other fields of surgery, found some use in urology This would appear to be another fortuitous application The histopathology of tissue reaction to this material has been adequately described elsewhere and indicates that it is rather quickly assimilated into a general pattern of fibrosis In this instance it would appear that its presence not only obliterates the cavity, but creates a sort of seal or patch over the urethral ostium Elimination of the need for meticulous dissection, surgical closure and concern about the urethral location of the stoma adds material solace Surgical trauma being minimal and operative time short, tissue healing and convalescence are expedited The same technique would appear logical for the exceedingly rare similar outcroppings of the male urethra Deferment, engendered by fear of fistula, is eliminated and abhorrent digital evacuation banished

CONCLUSIONS

A new technique is presented, utilizing oxycel packing, as a serviceable and simple means of ablating diverticulum of the female urethra

Absorbable material, of this type, apparently obliterates the cavity and seals the urethral communication by a process of fibrotic assimilation

Tissue response to this material eliminates the usual concern about sphincter-stoma relationship and ramifications of the sac

This type of ablation appears applicable for most periurethral cysts or diverticula in either the female or male

The technique is simple, short, tissue trauma minimal, and convalescence brief

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ROLE OF STRIATED MUSCLE IN URINATION

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Micturition is a complicated act involving smooth as well as striated muscles the function of each type of muscle has been a controversial subject from the earliest experiments on urination[1] to the present era One group of observers[2, 3] believes that micturition can be started as well as stopped by direct cortical control over bladder smooth muscle The other school which includes Galen, contends that activity of striated muscle is necessary for the voiding of urine Recent indirect evidence obtained by fluoroscopy and cinefluorography have led some investigators[4] to state that the voluntary mechanism for starting or stopping urination is mediated *entirely* through striated muscles Hinman and co-workers,[5] also on the basis of cinefluorography, disagree with this conclusion

In an effort to resolve this controversy we have conducted experiments[6] in humans to determine the part played by the striated perineal muscles in micturition It was found that paralysis of the perineal musculature obtained by bilateral pudendal nerve block did not affect initiation of urination nor did it produce incontinence except in one patient who had undergone prostatectomy, these observations are in agreement with previous work[7, 8] However, the amount of time necessary to stop urination during pudendal block was increased from a normal of 1–2 seconds to 8–10 seconds, this finding has not been noted previously

Since some research workers feel that the abdominal and diaphragmatic musculature forms a part of the voluntary mechanism necessary for control of micturition, it was decided to carry the investigation a bit further and produce complete flaccid paralysis of all of the skeletal muscle of the human body Under these circumstances it was hoped that an unequivocal answer could be obtained relative to the function of striated muscle in urination

METHOD

The muscle relaxants D-tubocurarine and succinylcholine were used in separate trials to produce flaccid paralysis of the striated muscle One female and 15

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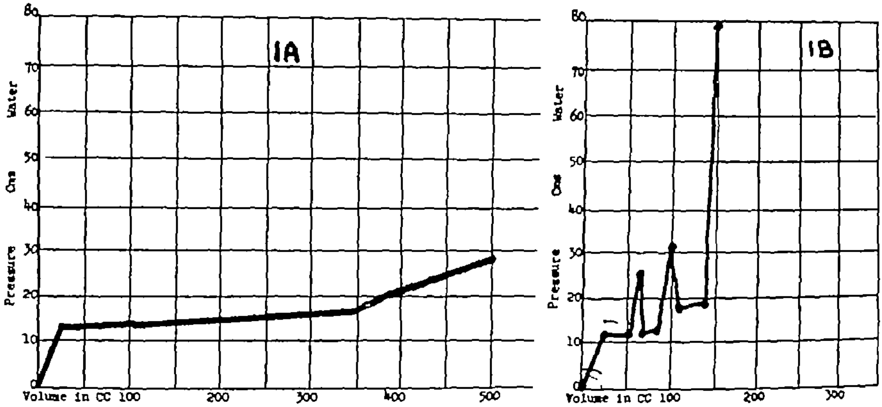

FIG 1

male patients served as subjects, they were fully conscious throughout the experiments

1) Since the effects of the skeletal muscle relaxants on the human autonomic nervous system are not known definitely at the present, it was considered necessary to ascertain these effects first Nine male patients with neurogenic bladders exhibiting uninhibited or uncontrolled contractions were selected as subjects for this part of the experiment Four of the patients exhibited reflex neurogenic bladders[9] associated with traumatic transverse myelitis while five subjects demonstrated uninhibited neurogenic bladders resulting from multiple sclerosis and cerebrovascular accidents Figure 1, *A* demonstrates the cystometrograph of a normal bladder while figure 1, *B* illustrates the cystometrograph of a bladder with uncontrolled contractions

Each patient was catheterized and several control cystometrographs obtained A muscle relaxant was administered then intravenously until flaccidity of all skeletal muscle was evident The bulbocavernosus reflex as described by Bors[10] was used to test for flaccidity of the perineal musculature Artificial respiration (intermittent manual compression of rebreathing bag) was necessary in all cases because of diaphragm and intercostal muscle paralysis Cystometrographs were repeated during the period of complete flaccid paralysis Four of the patients were administered both succinylcholine and D-tubocurarine on different occasions while the remaining five were given only succinylcholine

2) When the experiments on the neurogenic bladders had been completed and evaluated, attention was directed toward the seven patients with normal bladders For several days prior to the experimental run, each patient was instructed to practice emptying the bladder in the supine position, this was done in order to accustom the patient to voiding in the posture assumed during complete flaccid paralysis On the day of the experimental run the patient was placed in the supine position, catheterized and the bladder filled with physiological saline In three of the patients the amount of fluid instilled was 300 ml , in the four other patients the amount instilled was governed by the patient's sensation of

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fullness and varied with the patient After the bladder was filled with fluid, the catheter was removed and the patient requested to initiate urination and then to stop it After the performance times were noted, the patient was paralyzed completely with succinylcholine or D-tubocurarine as previously described When complete skeletal flaccidity was present the patient was catheterized again the bladder filled with the same amount of fluid used in the control micturition and the catheter withdrawn The patient was asked to initiate and then to inhibit micturition The time intervals taken to carry out the commands were noted Several patients were placed in the semi-upright position before being requested to void in order to observe continence

RESULTS

1) Amounts of succinylcholine and D-tubocurarine necessary to produce flaccidity of all striated muscle were insufficient to abolish or significantly impair the uncontrolled contractions of the patients with neurogenic bladders Cystometrographs from a typical experiment are illustrated in figure 2 A is the control cystometrograph and B is the cystometrograph obtained during succinylcholine administration Observe that the two graphs are essentially identical Muscle relaxants did not impair transmission of nerve impulses over the parasympathetic pathways to the bladder

2) Of the patients with normal bladders five were able to start micturition within two seconds after command while the remaining two required five seconds to initiate urination All of the normal patients could stop urination within two seconds after request

After complete flaccid paralysis with one or the other of the muscle relaxants all of the patients could initiate urination within their control time interval i e , 2–5 seconds However, none of the patients could inhibit urination within the control time of 2 seconds but required 8–15 seconds for cessation of micturition Measurement of voided fluid in these patients indicated that inhibition of urination had been accomplished before 75 per cent of the instilled fluid volume had been evacuated It was observed that after the bladders had been filled with saline, leaking of fluid from the urethral meatus did not occur either in the supine or semi-erect positions

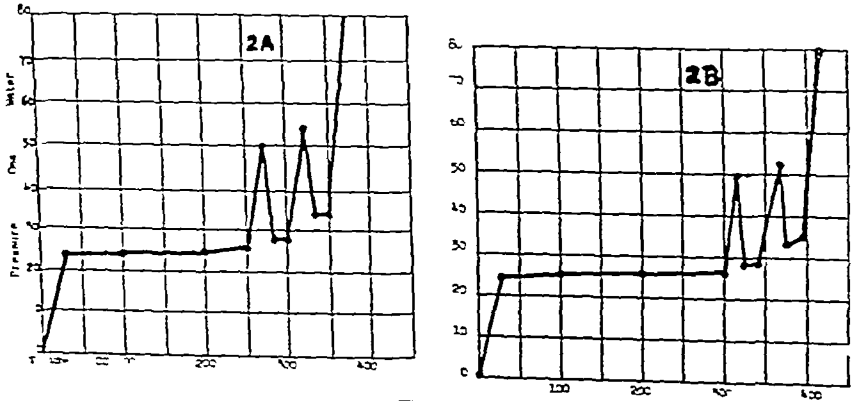

FIG. 2

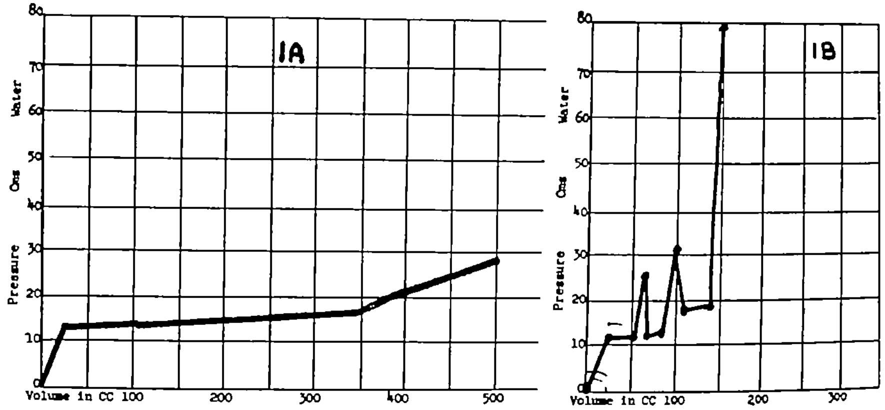

Fig 1

male patients served as subjects, they were fully conscious throughout the experiments

1) Since the effects of the skeletal muscle relaxants on the human autonomic nervous system are not known definitely at the present, it was considered necessary to ascertain these effects first Nine male patients with neurogenic bladders exhibiting uninhibited or uncontrolled contractions were selected as subjects for this part of the experiment Four of the patients exhibited reflex neurogenic bladders[9] associated with traumatic transverse myelitis while five subjects demonstrated uninhibited neurogenic bladders resulting from multiple sclerosis and cerebrovascular accidents Figure 1, *A* demonstrates the cystometrograph of a normal bladder while figure 1, *B* illustrates the cystometrograph of a bladder with uncontrolled contractions

Each patient was catheterized and several control cystometrographs obtained A muscle relaxant was administered then intravenously until flaccidity of all skeletal muscle was evident The bulbocavernosus reflex as described by Bors[10] was used to test for flaccidity of the perineal musculature Artificial respiration (intermittent manual compression of rebreathing bag) was necessary in all cases because of diaphragm and intercostal muscle paralysis Cystometrographs were repeated during the period of complete flaccid paralysis Four of the patients were administered both succinylcholine and D-tubocurarine on different occasions while the remaining five were given only succinylcholine

2) When the experiments on the neurogenic bladders had been completed and evaluated, attention was directed toward the seven patients with normal bladders For several days prior to the experimental run, each patient was instructed to practice emptying the bladder in the supine position, this was done in order to accustom the patient to voiding in the posture assumed during complete flaccid paralysis On the day of the experimental run the patient was placed in the supine position, catheterized and the bladder filled with physiological saline In three of the patients the amount of fluid instilled was 300 ml , in the four other patients the amount instilled was governed by the patient's sensation of

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[9] Nesbit, R M , Lapides, J and Baum, W C Fundamentals of Urology Ann Arbor J W Edwards, 1953

[10] Bors, E , Comarr, A E and Moulton, S H The role of nerve blocks in management of traumatic cord bladders J Urol **63** 653, 1950

fullness and varied with the patient After the bladder was filled with fluid, the catheter was removed and the patient requested to initiate urination and then to stop it After the performance times were noted, the patient was paralyzed completely with succinylcholine or D-tubocurarine as previously described When complete skeletal flaccidity was present, the patient was catheterized again, the bladder filled with the same amount of fluid used in the control micturition and the catheter withdrawn The patient was asked to initiate and then to inhibit micturition The time intervals taken to carry out the commands were noted Several patients were placed in the semi-upright position before being requested to void in order to observe continence

RESULTS

1) Amounts of succinylcholine and D-tubocurarine necessary to produce flaccidity of all striated muscle were insufficient to abolish or significantly impair the uncontrolled contractions of the patients with neurogenic bladders Cystometrographs from a typical experiment are illustrated in figure 2 A is the control cystometrograph and B is the cystometrograph obtained during succinylcholine administration Observe that the two graphs are essentially identical Muscle relaxants did not impair transmission of nerve impulses over the parasympathetic pathways to the bladder

2) Of the patients with normal bladders five were able to start micturition within two seconds after command while the remaining two required five seconds to initiate urination All of the normal patients could stop urination within two seconds after request

After complete flaccid paralysis with one or the other of the muscle relaxants all of the patients could initiate urination within their control time interval, i e , 2–5 seconds However, none of the patients could inhibit urination within the control time of 2 seconds but required 8–15 seconds for cessation of micturition Measurement of voided fluid in these patients indicated that inhibition of urination had been accomplished before 75 per cent of the instilled fluid volume had been evacuated It was observed that after the bladders had been filled with saline, leaking of fluid from the urethral meatus did not occur either in the supine or semi-erect positions

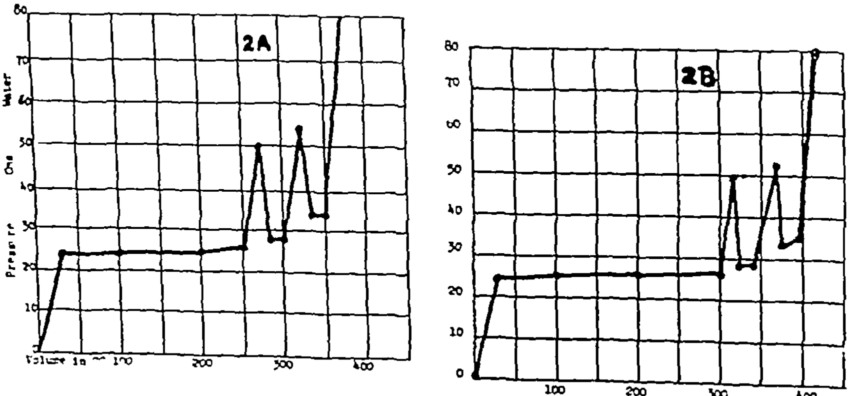

FIG 2

DISCUSSION

In 1933 Denny-Brown and Robertson[2] studied micturition in three normal patients by means of endoscopy, cystometry and sphincterometry They concluded that micturition is initiated by a voluntary contraction of the vesical smooth muscle itself The activity of such striated muscles as perineal, abdominal and diaphragmatic during initiation of micturition, were considered associated movements and not directly connected with the starting of urination These investigators observed that the vesical neck or sphincter opened only after bladder muscle had started to contract The external urethral sphincter in turn dilated following detrusor contraction and opening of the vesical neck In no instance was the striated external sphincter observed to open before the bladder had started to contract

They noted also, that with abrupt inhibition of urination, the external urethral sphincter constricted rapidly followed by a gradual cessation of vesical muscle contraction and slow closure of the vesical neck

The observations made during the present investigation support the findings of Denny-Brown and Robertson in every respect With all skeletal muscle paralyzed normal patients were observed to start and stop micturition voluntarily This phenomenon was noted not only in the acute experiments described but also in a patient suffering from tetanus who was kept paralyzed with anectine in a respirator for a period of four days [11]

Although the subjects could stop urination voluntarily during flaccid paralysis, the inhibition was a slow process (10–15 seconds) as compared with the time taken to halt urination in the control period (less than 2 seconds) This agrees with Denny-Brown's observation of the slow, gradual termination of bladder contraction and vesical neck closure after inhibition of micturition

Dortenmann and Bauer[12] conducted experiments on bladder function with muscle relaxants also, and although their findings differed in many respects from ours, they too observed *voluntary* initiation and inhibition of urination in completely paralyzed human subjects

Incontinence of urine was not observed during paralysis of striated muscles This observation confirms our findings with pudendal block and is in accord with previous experiments[6] which indicated that urinary continence can be maintained by either the vesical neck or external urethral sphincter Both must be injured to result in a typical "dripping type" of urinary incontinence

CONCLUSIONS

Micturition can be initiated and terminated *voluntarily* without the use of any striated muscle in the human body

Striated muscle is necessary for the sudden, rapid inhibition of urination

Urinary continence can be maintained by the vesical neck (internal vesical sphincter) alone in the absence of functioning striated perineal musculature

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[11] Vial, B A Succinylcholine and artificial respiration in the treatment of tetanus Report of a case U Mich Med Bull , **21** 123, 1955

[12] Dortenmann, S and Bauer, K M Untersuchungen über den Einfluss der quergestreiften Muskulatur auf die Blassenfunktionen mit Hilfe eines Muskelrelaxans Die Medizinische **15** 528, 1955

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PEYRONIE'S DISEASE TREATMENT BY THE LOCAL INJECTION OF METICORTELONE AND HYDROCORTISONE

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Plastic induration of the corpora cavernosa, or Peyronie's disease, was first described 200 years ago and has been one of the enigmas of medicine ever since It may not be so important clinically to the general public as arteriosclerotic heart disease, but to the man afflicted it is certainly as disturbing The incidence is not so rare as it was once thought to be, over 1200 cases having been reported by 1949 Encouraging reports on the effective use of cortisone and hydrocortisone injections in the treatment of this condition stimulated our interest, at the Squier Urological Clinic, to evaluate steroidal injection therapy more fully For the past 18 months meticortelone (prednisolone) and hydrocortisone have been injected locally into 13 cases of Peyronie's disease The following is a report of the results obtained in our steroid-treated cases as compared with those seen in other cases of ours treated by different methods

HISTORY

This condition was first described by the great French physician of Louis 14, Franciscura de la Peyronie, in 1743 He did not recognize the disease as we know it today (a fibrous plaque lying between Buck's fascia and the tunica albuginea of the corpora cavernosa) but rather noted it in his article on "Some Obstacles Opposing the Natural Ejaculation of Semen" He described "rosary beads" along the dorsum of the penis which resulted in a dorsal deflection of the organ when it became turgid

This disease has been called plastic induration of the corpora cavernosa, fibrous cavernositis, fibrous sclerosis, and fibrous plaques of the penis Prior to World War I this condition was frequently called Van Buren's disease because of Van Buren's and Keyes' report in the New York Medical Journal in 1874 Only in more recent years has Peyronie's name been held synonymous with this disturbance

ETIOLOGY

Although a great deal has been written concerning the origin of Peyronie's disease, very little concrete evidence has ever been found Hertzler reports that in 1847 Ricord reviewed this problem and concluded that syphilis, trauma, and inflammation were the basic causes Tüffier described degeneration of connective tissue elements, similar to that found in joints and aponeuroses, as in gout, diabetes mellitus, and arthritis In the German literature, Zur Verth, Scheele, and Rothschild attribute the origin to slight trauma encountered during coitus This implies the rupture of small blood vessels in the tunica albuginea with

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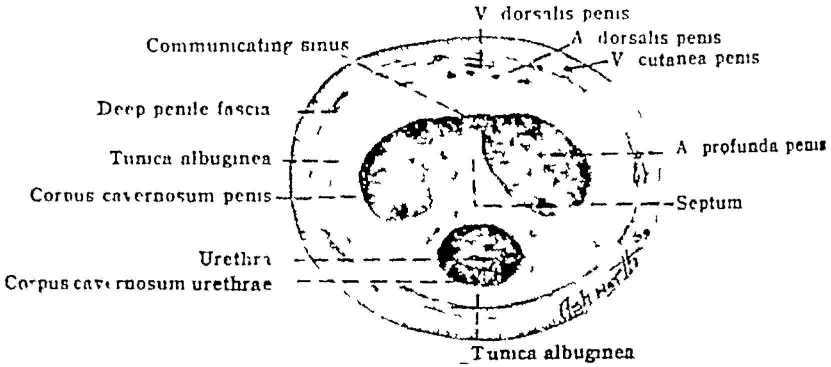


FIG 1 Cross section of penis From Morris' Human Anatomy A Complete Systemic Treatise, edited by J Parsons Schaeffer, 10th ed Philadelphia Blakiston Co , 1942

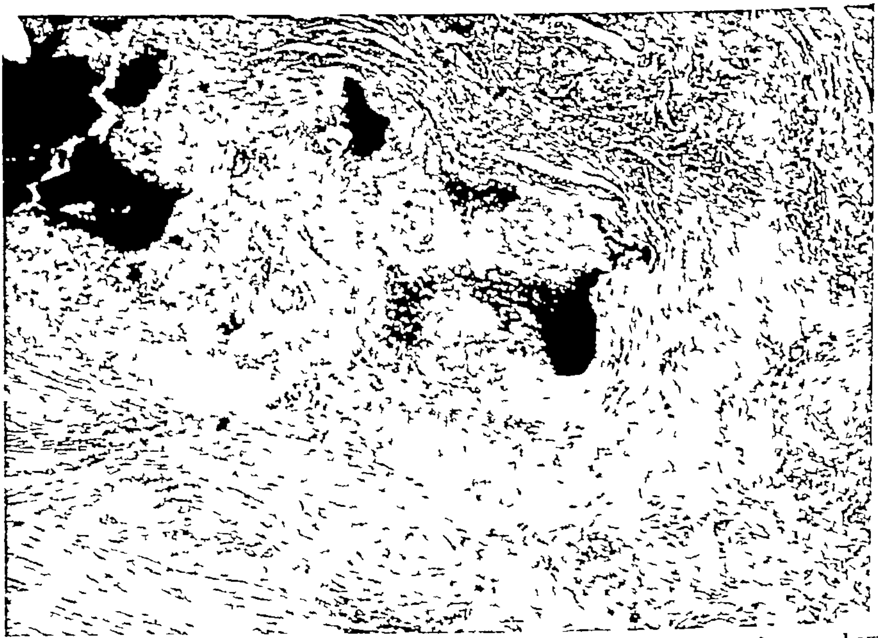


FIG 2 Dense bundles of hyalinized connective tissue with sparse nuclei are shown Calcific deposits are present with trabeculation of bony tissue

subsequent replacement of the hematoma by fibrosis, and later, in a few cases, deposition of calcium salts

Peyronie's disease and Dupuytren's contracture are similar chronic sclerosing inflammations of the fascia with a tendency to recur following surgical removal Siebrecht found only 10 per cent of the Peyronie's cases with associated Dupuytren's contractures The only similarities between the two conditions are "heredity, senility, and a constitutional predisposition to sclerosing processes in connective tissue " Further observation and investigation are still needed to clarify its origin

PATHOLOGY

The commonest location for a plaque is behind the coronal sulcus, straddling the corpora cavernosa It lies between Buck's fascia and the tunica albuginea, and inferior to the dorsal vessels and nerves (fig 1) A fibrous band (chordee) may be seen involving the central septum and adhering to the tunica albuginea Chordee may be seen with or without a plaque, occasionally the spongy tissue may become involved

The initial fibrous lesion develops rather insidiously and relatively rapid over several months, and then grows slowly In a few cases spontaneous regression has been noted Calcification is seen not infrequently, but when present it is in the later stages Ulceration and malignancy have never been reported

Microscopically, fibrocytes are found in the plaques as well as in the tunica albuginea Because of this, many people believe that the tunica must be the site of origin for the plaques The main picture is one of proliferation and hyperplasia of connective tissue running from early cellular development to old scarring tissue The plastic induration may well be due to degeneration of the tunica albuginea It is thought by some that the connecting tissue originates in the adventitia of the small blood vessels following rupture of the latter (Figure 2 illustrates a typical microscopic cross section)

SYMPTOMS

The initial presenting complaints are those of painful penile erections accompanied by curvature The deflection is usually dorsal Coitus may be impaired and, not infrequently, is impossible With flaccidity of the organ no discomfort is felt, so that the patient usually does not seek medical advice until after noting that pain is felt with turgidity

TREATMENT

Every urologist is faced at one time or another with the problem of treating a case of Peyronie's disease His predicament is that whenever the etiology of a disease remains obscure, the treatment also is nonspecific Each method claims its cures, yet no one type, or combination of types, can be considered fool-proof Treatment for this condition is, therefore, varied and falls into the following classifications 1) x-ray therapy, 2) radium, 3) diathermy, 4) massage, 5) fibrolysin (hyaluronidase), 6) local drug applications, 7) electrolysis and ultraviolet radiation, 8) internal medication, 9) surgery, and 10) steroidal injections

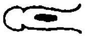
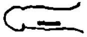
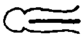
X-ray therapy in small doses is supposed to soften the fibrous tissue, however, in our 13 cases only 2 patients were helped by this method (table 8) Radium and x-ray produce similar reactions in tissue, and if given in small doses, good results may be achieved Burford's series of 47 cases, treated with radium, showed 21 per cent cures, 51 per cent improved, and 13 per cent without changes

Diathermy and massage have been recommended because of the effects of increased circulation Wesson believes that every patient with Peyronie's disease should own a diathermy machine, but few people have been able to report highly successful changes with use of this machine

TABLE 1

Key

Present = X
Absent = 0̄
Unknown = ?
1 Cauda = Cauda Equina Epidermoid Cyst
2 Diabt = Diabetes Mellitus
3 Dupt = Dupuytren Contractures
4 "G C" = Gonorrheal Urethritis
5 HCVD = Hypertensive Cardiovascular Disease
6 O D = Daily
O W = Weekly
7 Osteo = Osteoarthritis
8 Prost = Prostatitis, Chronic
9 Prostat = Prostatectomy
10 Pul Tbc = Pulmonary Tuberculosis
11 Rheum = Rheumatoid Arthritis
12 Strict = Urethral Stricture
13 Syph = Syphilis
14 V D = Venereal Disease

Unit No	History					Laboratory		Lesion Diagram	Lesion Description						Pain c̄ Erection	Coitus Unsatis
	Age at onset	Symptoms for	V D	Penile injury	Chronic diseases	Serology	Urine		Dorsal fascia	Corpora cavernosa	Plaque	Chordee	Calcium	Type of curvature		
1) 672528	50	2 yrs	"G C"	25 yrs before	0̄	0̄	0̄		X	0̄	X	0̄	X	Dorsal	X	X
2) 981233	61	3 mos	0̄	0̄	0̄	0̄	0̄		0̄	X	0̄	X	?	Ventral	X	?
3) 210026	54	7 mos	"G C" Syphil	0̄	Pulm Tbc 1930	Positive	0̄		X	X	0̄	0̄	0̄	Dorsal & lateral	X	?

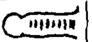
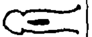
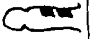
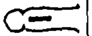
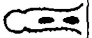
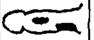
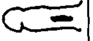
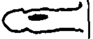
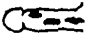
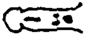
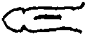
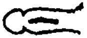
4) 020070	51	8 mos	"G C" Syph	0̄	0̄	Positive	0̄		✓	0̄	X	0̄	0̄	Dorsal	0̄	?
5) 280271	51	6 mos	0̄	Prostat	Dupt	0̄	Pyuria		0̄	✓	0̄	0̄	?	Ventral	X	?
6) 036392	62	5 mos	"G C" Syph	0̄	0̄	0̄	?		X	X	X	0̄	0̄	Dorsal	X	X
7) 106272	12	1 days	0̄	0̄	0̄	?	?		X	0̄	X	0̄	0̄	Dorsal	X	?
8) 885011	77	2 mos	0̄	0̄	?	?	0̄		X	X	X	?	0̄	Dorsal	X	?
9) 817137	33	6 mos	0̄	0̄	Rheum	0̄	Pyuria		X	X	X	X	0̄	Dorsal	X	X
10) 035333	10	8 mos	0̄	0̄	Diabt	0̄	0̄		X	0̄	X	0̄	?	Dorsal	X	?
11) 021625	50	5 mos	"G C"	0̄	Dupt	?	?		X	X	X	0̄	?	Dorsal	X	?
12) 782305	56	2 mos	"G C"	0̄	Osteo	0̄	0̄		X	X	X	0̄	0̄	Dorsal & rt lat	X	0̄
13) 078620	51	12 mos	"G C"	0̄	0̄	0̄	0̄		0̄	X	0̄	0̄	X	Dorsal lt lat	0̄	?
14) 075711	53	5 mos	"G C"	0̄	Prost	0̄	0̄		?	X	?	X	0̄	Lat rt	0̄	?
15) 703705	54	5 mos	?	0̄	0̄	0̄	0̄		0̄	0̄	0̄	X	?	Ventral lat lt	0̄	?

TABLE 2

Unit No Yr Rx	Type of Treatment		No Treat ments	Results of Therapy					
	Type	Dose		Duration of Rx	Penile Pain Changes	Curvature Changes	Coitus	Plaque Changes	General Statement
1)	1 Surgical excision	—	—	—	Same	Same	?	Recurred	Unchanged
672528	2 X ray	1500 R	10	10 wks	$\bar{0}$	No erections	$\bar{0}$	None	Unchanged
(1942–1951)	3 Testosterone	50 mg O W	12	4 wks	$\bar{0}$	Poor erections	±	None	Unchanged
2) 981233 (1944)	Circumcision	—	—	—	?	?	?	?	?
3) 249026 (1937)	X ray	600 R	3	3 wks	?	?	?	?	Unchanged
4)	1 Testosterone	10–40 mg o d	120	3 mos	$\bar{0}$	$\bar{0}$	$\bar{0}$	None	Unchanged
317209	2 Cortisone	200 mg o d	9	9 dys	$\bar{0}$	$\bar{0}$	$\bar{0}$	None	Unchanged
(1950)	3 X ray	800 R	8	8 wks	$\bar{0}$	$\bar{0}$	$\bar{0}$	None	Unchanged
	4 Alidase	500 U	3	2 wks	$\bar{0}$	$\bar{0}$	$\bar{0}$	None	Unchanged
5) 280274 (1937)	None	—	—	—	?	?	?	None	Improved slightly, 5 yrs
6)	1 X ray	1400 R	7	2 mos	$\bar{0}$	$\bar{0}$	$\bar{0}$	None	Unchanged
396932	2 Testosterone	70 mg o w	10	3 wks	$\bar{0}$	$\bar{0}$	X	None	Good for 2 mos
(1947)	Testosterone	70 mg o w	9	3 wks	$\bar{0}$	$\bar{0}$	$\bar{0}$	None	Fair
7)	1 Testosterone	75 mg o w	21	7 wks	$\bar{0}$	Recurred	X	Softer, smaller	Fair
196272 (1948)	2 X ray	800 R	8	8 wks	—	—	—	None	Unchanged

8) 885644	1 X ray 2 Testosterone	1800 R 75 mg o w	9 15	4 wks 5 wks	0̄ Loss	0 0̄	0 0̄	None None	Unchanged Unchanged
9) 817437 (1946–1949)	1 X ray 2 Testosterone Testosterone	1000 R 50 mg o w 50 mg o w	4 9 10	4 wks 4 wks 4 wks	0 Loss Loss	0 0̄ 0̄	0̄ X 0̄	None None None	Unchanged Fair Worse
10) 935333 (1949)	1 Testosterone 2 X ray	20 mg o d 800 R 800 R	14 4 4	2 wks 4 wks 4 wks	0̄ Loss Loss	0̄ 0̄ 0̄	— — —	0̄ 0̄ 0̄	Unchanged Unchanged Unchanged
11) 921625 (1948)	X ray	800 R	4	4 wks	0̄	0̄	—	0	Unchanged
12) 782395 (1946)	X ray	1000 R	5	5 wks	0̄	0̄	X	Reduced to one	Excellent 4 yrs
13) 678620 (1942)	1 X ray X ray	1500 R 1500 R	7 3	5 wks 10 dys	— —	0̄ 0̄	— —	0̄ 0̄	Unchanged Unchanged
14) 675744 (1944)	X ray	800 R	3	3 wks	?	?	?	?	?
15) 793795 (1945)	X ray	1000 R	5	4 wks	0̄	Improved	?	0̄	Good—9 mos

Fibrolysins (hyaluronidase) have been used with systemic and local injection without consistent improvements, and the local applications of camphor, iodine, iodoform, mercury, etc have done very little for the relief of this condition The same may be said for electrolysis and ultraviolet radiation

Internal medication programs such as arsenicals, testosterone, iodine compounds, sodium phosphates, and vitamin E have been tried, but again with varied results Scott showed an 80 per cent response of some degree in 33 cases with use of tocopherol In our series of 28 cases, testosterone was used in 7 (table 8) with 3 responses, one of which was permanent

Lowsley has been the champion for surgical excision of the plaques, provided that they have not extended into the median sagittal plane of the corpora He reports 39 cures in 50 patients (78 per cent), which is a formidable rate No one else has been able to duplicate these figures In one of four cases of excision a recurrence developed with symptoms as severe as those experienced by the patient preoperatively

The first reference in the literature to the use of cortisone in the treatment of Peyronie's disease is made by Teasley who, in 1952, reported its use to the Dallas Urological Group In fibroblastic cultures, cortisone delays fibroplasia by inhibiting the genesis of the fibrils This effects shrinkage of the fibroblasts without damaging the elastic fibers themselves With these facts in mind, Teasley instituted the use of cortisone and obtained good results in a few cases, while Bodner's group showed 15 out of 16 cases improved with cortisone and hydrocortisone Encouraged by the results of these reports, we at the Squier Urological Clinic started 18 months ago to treat our series of 14 cases with hydrocortisone and meticortelone (prednisolone)

PRESENTATION OF CASES

Tables 1 to 4 give the complete details on all 28 cases seen by us since 1937 Case 9 is reported twice because he was treated in both series Table 5 summarizes past histories and shows that there is no predominant associated disease Symptoms had been present for 10 6 months, with the average being 7 0 months for the group treated by x-ray, and 14 2 months for the steroidal-treated group Table 6 illustrates the age incidence as compared with that reported by Burford and Lowsley The fifth decade seems to have the highest incidence of the disease, with the fourth and fifth decades together totaling 78 per cent in our series Our average age was 53 2 years, thus comparing favorably with Lowsley's average age of 50 years

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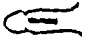
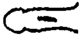
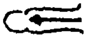
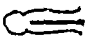
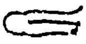
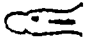
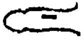
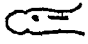
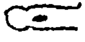
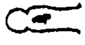
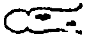
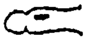
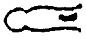
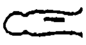
	Age at Onset	Symptoms for	V D	Penile Injury	Chronic diseases	Serology	Urine		Dorsal fascia	Corpora cavernosa	Plaque	Chordee	Calcium	Type of curvature		
1) 120510	57	8 mos	0̄	0	Chronic prostatitis	0̄	0̄		X	0	0̄	0̄	0̄	Dorsal	X	X
2) 008201	17	8 mos	"G C"	0	Ca Rectum 1951	?	0		X	0	0̄	0	X	Dorsal	X	0̄
3) 181155	15	11 mos	0̄	0	1 Osteo 2 Prost	0	0̄		X	0̄	X	X	X	Dorsal	X	0̄
4) 122388)	51	12 mos	"G C"	0̄	1 Strict 2 Gout	0	0̄		X	0̄	0̄	X	0̄	Dorsal	0̄	X
5) 817137	11	8 yrs	0	0̄	1 Rheum 2 Prost 3 Strict	0̄	Pyuria		X	X	X	X	X	Dorsal	0̄	X
6) 220010	50	2 mos	Syphilis	0̄	Prost	Positive	Pyuria		X	0̄	X	0̄	0̄	Dorsal	0̄	0̄
7) 217021	50	6 mos	0	0	0̄	0	0		X	0	X	0̄	X	Dorsal	X	0̄
8) 080170	30	6 mos	0̄	0	Gauda	0̄	0̄		X	0̄	X	0̄	0̄	Dorsal	X	0̄
9) 220801	11	2 mos	0̄	0̄	0̄	0̄	?		X	0̄	X	0̄	X	Dorsal lator	0̄	0̄
10) 211010	16	2 yrs	0̄	0̄	0	0̄	0̄		X	0̄	X	0̄	0̄	Dorsal	X	0̄
11) 243200	63	8 mos	0̄	?	Pul Tbc	0̄	0̄		X	0̄	X	0̄	0̄	Dorsal	X	0̄
12) 107105	56	9 mos	0	?	HCVD	0̄	0		X	0	X	0̄	0̄	Lateral	0̄	X
13) 870841	50	6 mos	0̄	0̄	0̄	0̄	0̄		X	0̄	X	0̄	0̄	Dorsal	X	?
14) 181625	53	5 mos	0̄	(?)	0̄	0̄	(?)		X	0̄	X	0̄	0̄	Dorsal	X	0̄

Fibrolysins (hyaluronidase) have been used with systemic and local injection without consistent improvements, and the local applications of camphor, iodine, iodoform, mercury, etc have done very little for the relief of this condition The same may be said for electrolysis and ultraviolet radiation

Internal medication programs such as arsenicals, testosterone, iodine compounds, sodium phosphates, and vitamin E have been tried, but again with varied results Scott showed an 80 per cent response of some degree in 33 cases with use of tocopherol In our series of 28 cases, testosterone was used in 7 (table 8) with 3 responses, one of which was permanent

Lowsley has been the champion for surgical excision of the plaques, provided that they have not extended into the median sagittal plane of the corpora He reports 39 cures in 50 patients (78 per cent), which is a formidable rate No one else has been able to duplicate these figures In one of four cases of excision a recurrence developed with symptoms as severe as those experienced by the patient preoperatively

The first reference in the literature to the use of cortisone in the treatment of Peyronie's disease is made by Teasley who, in 1952, reported its use to the Dallas Urological Group In fibroblastic cultures, cortisone delays fibroplasia by inhibiting the genesis of the fibrils This effects shrinkage of the fibroblasts without damaging the elastic fibers themselves With these facts in mind, Teasley instituted the use of cortisone and obtained good results in a few cases, while Bodner's group showed 15 out of 16 cases improved with cortisone and hydrocortisone Encouraged by the results of these reports, we at the Squier Urological Clinic started 18 months ago to treat our series of 14 cases with hydrocortisone and meticortelone (prednisolone)

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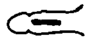
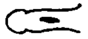
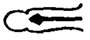
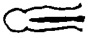
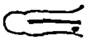
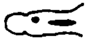
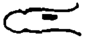
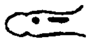
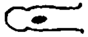
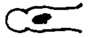
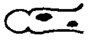
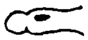
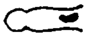
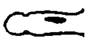
1) 126540	57	8 mos	0̄	0̄	Chronic prostatitis	0̄	0̄		X	0̄	0̄	0̄	0̄	Dorsal	X	X
2) 998293	47	8 mos	"G C"	0̄	Ca Rectum 1953	?	0̄		X	0̄	0̄	0̄	X	Dorsal	X	0̄
3) 184455	45	11 mos	0̄	0̄	1 Osteo 2 Prost	0̄	0̄		X	0̄	X	X	X	Dorsal	X	0̄
4) 122388)	51	12 mos	"G C"	0̄	1 Strict 2 Gout	0̄	0̄		X	0̄	0̄	X	0̄	Dorsal	0̄	X
5) 847137	41	8 yrs	0̄	0̄	1 Rheum 2 Prost 3-Strict	0̄	Pyuria		X	X	X	X	X	Dorsal	0̄	X
6) 220910	50	2 mos	Syphilis	0̄	Prost	Positive	Pyuria		X	0̄	X	0̄	0̄	Dorsal	0̄	0̄
7) 217921	50	6 mos	0̄	0̄	0̄	0̄	0̄		X	0̄	X	0̄	X	Dorsal	X	0̄
8) 080470	30	6 mos	0̄	0̄	Cauda	0̄	0̄		X	0̄	X	0̄	0̄	Dorsal	X	0̄
9) 226801	44	2 mos	0̄	0̄	0̄	0̄	?		X	0̄	X	0̄	X	Dorsal later	0̄	0̄
10) 231930	46	2 yrs	0̄	0̄	0̄	0̄	0̄		X	0̄	X	0̄	0̄	Dorsal	X	0̄
11) 233260	63	8 mos	0̄	?	Pul Tbc	0̄	0̄		X	0̄	X	0̄	0̄	Dorsal	X	0̄
12) 167105	56	9 mos	0̄	?	HCVD	0̄	0̄		X	0̄	X	0̄	0̄	Lateral	0̄	X
13) 879831	59	6 mos	0̄	0̄	0̄	0̄	0̄		X	0̄	X	0̄	0̄	Dorsal	X	?
14) 184625	53	5 mos	0̄	(?)	0̄	0̄	(?)		X	0̄	X	0̄	0̄	Dorsal	X	0̄

TABLE 4

Unit No Yr Rx	Type of Treatment		Results of Treatment						
	Type	Dose	No of Rx	Duration of Rx	Penile Pain Changes	Curvature Changes	Coitus	Plaque Changes	General Statement
1) 126519 (1954–55)	1 Hydrocortisone 2 Meticortelone	25 mg 25 mg	11 4	2 mos 1 mo	Improved No pain	Same Same	Poor Poor	Softer Softer	Fair Fair
2) 998293 (1954–55)	1 Hydrocortisone 2 Meticortelone	25 mg 25 mg	31 9	7 mos 2 mos	Absent Absent	Improved 50% Improves slowly	Present Present	Broken-up softer Softer	Good Good
3) 184155 (1954–55)	1 Hydrocortisone 2 Meticortelone	25 mg 25 mg	30 7	8 mos 2 mos	Same Same	Same Same	Poor Poor	Same Same	Unchanged Unchanged
4) 122388 (1954)	Hydrocortisone	50 mg	12	5 mos	Same	Same	Poor	Same	Unchanged
5) 847137 (1954–55)	1 Hydrocortisone 2 Meticortelone	50 mg 25 mg	25 5	8 mos 2 mos	Same Same	Same Same	Impotent Impotent	Same Same	Unchanged Unchanged
6) 220940 (1955)	Meticortelone	25 mg	18	7 mos	Absent	Improved 50%	Present	Softer	Good
7) 217921 (1955)	1 Hydrocortisone 2 Meticortelone	50 mg 25 mg	17 7	5 mos 4 mos	Absent Absent	Improved 90% Same	Present Present	Softer & smaller Softer & smaller	Excellent Excellent

8) 080470 (1955)	Hydrocortisone	50 mg	2	2 weeks	Absent	Same	Present	Same	—
9) 220801 (1955)	1 Hydrocortisone 2 Meticortelone	50 mg 25 mg	5 16	1 mo 6 mos	Absent Absent	Developed Same	Present Present	Same Same	Unchanged Unchanged
10) 231930 (1955)	Meticortelone	25 mg	8	4 mos	Absent	Slightly less	Present	Same	Fair
11) 233260 (1955)	Meticortelone	25 mg	9	4 mos	Same	Same	Present	Same	Unchanged
12) 167105 (1955)	Meticortelone	25 mg	8	2 mos	Absent	Same	Poor	None	Unchanged
13) 870841 (1955)	Meticortelone	20 mg p o	14	2 weeks	?	?	?	?	?
14) 181025 (1955)	Meticortelone	25 mg	12	3 mos	Same	Same	Present	None	Unchanged

TABLE 5

History

1 Venereal diseases				
Syphilis				4
Gonorrhea				10
2 Penile injuries				
Prostatectomy				1
3 Chronic diseases				
a chronic prostatitis	5	f	gout	1
b arthritis	3	g	diabetes mellitus	1
c Duputyren's	2	h	carcinoma sigmoid	1
d urethral strictures	2	i	H C V D	1
e pulmonary tuberculosis	2	j	cauda equina cyst	1

TABLE 6

	Patients	Years				
		30–40	40–50	50–60	60–70	70–80
P H	28	2 (7%)	6 (21%)	16 (57%)	3 (11%)	1 (4%)
Burford	47	3 (4%)	14 (19%)	27 (38%)	24 (34%)	1 (1%)
Lowsley	33	4 (8%)	11 (22%)	25 (50%)	7 (14%)	0

TABLE 7

		%
Location of Condition —		
a Plaques	19	(68%)
b Chordee	7	(25%)
c Corpus cavernosa	11	(40%)
d Calcium (x ray)	7	(25%)
Type of Curvature —		
Dorsal	20	(71%)
Dorsal lateral	3	(11%)
Ventral	3	(11%)
Lateral	2	(7%)

TABLE 8

Therapy	No Cases	Exc	Good	Fair	Temp Relief	Unchanged	% Improved
1 X-ray	13	1	1	—	—	11	15 3%
2 Steroid	12	1	2	2	—	7	41 6%
3 Testosterone	7	—	—	2	1	4	15 3%
4 Surgery	1	—	—	—	—	1	0 0%

Table 8 summarizes the different types of therapy with their results Fourteen patients were started on either hydrocortisone or meticortelone Two patients were lost to followup, and therefore are not included for long-term studies Five of the 12 cases (41 per cent) obtained fair to excellent improvement These compare with Bodner's figures The poor response of the plaques (table 9) will explain why there were not greater changes in the curvature This is not as high

TABLE 9 *Functional results*

	Improved		Unchanged	Total
1 Curvature	4 (30 7%)		9 (69 3%)	13
2 Pain c̄ erections	8 (61 5%)		5 (38 5%)	13
	Marked Improv	Sl. Improv	Unchanged	
1 Plaques	4 (30 7%)	7 (53 8%)	2 (15 5%)	13

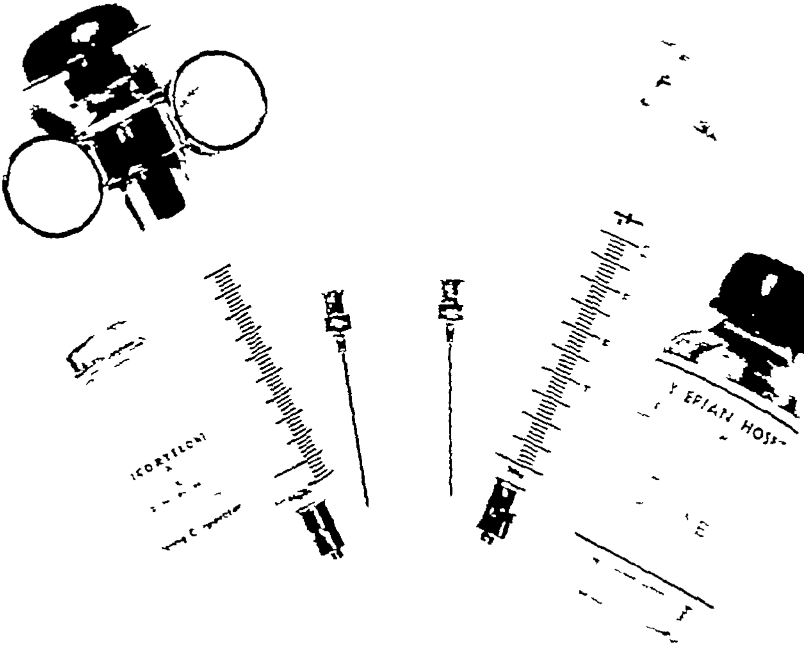


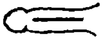
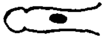
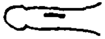
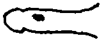
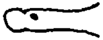
FIG 3 Ten cubic centimeter Luer Lok syringe with finger holders, No 18 gauge needle, 10 cc syringe 2 per cent novocain, and meticortelone

an incidence for relief of the curvature as was expected, although higher than that in our cases treated by x-ray (15 3 per cent), testosterone (15 3 per cent), or surgery (0 0 per cent) No appreciable difference could be found in the results of either hydrocortisone or meticortelone (table 10) as 117 injections were made with hydrocortisone and 133 with meticortelone

TECHNIQUE FOR INJECTIONS

A few pertinent factors should be mentioned as our series contained over 250 injections of steroids with 220 total penile anesthesia The local injection of novocain into the plaque, as advocated by Teasley and Bodner, did not afford enough anesthesia in our cases Total penile anesthesia was instituted

TABLE 10 *Steroid therapy*

History	Drug	Lesion	No of Rx	Penile Pain Changes	Curvature Changes	Coitus	Plaque Changes	Results
1 #126549	1) Hydro 2) Meti	 *(ca 0)	11 4 — 15	Improved No pain	Same Same	Poor Poor	Softer Softer	Fair Fair
2 #998293	1) Hydro 2) Meti	 (ca ?)	31 9 — 40	Relieved None	Improved (50%) Improving	Present Present	Softer Softer	Good Good
3 #217921	1) Hydro 2) Meti	 (ca +)	17 7 — 24	Relieved No pain	Improved (90%) Improving	Present Present	Softer, smaller Status quo	Excellent Excellent
4 #231920	Meti	 (ca 0)	8	Relieved	Slightly improved	Present	Same	Fair
5 #220940	Meti	 (ca 0)	18	Relieved	Improved (50%)	Present	Softer	Good

* *Key* ca = calcium

with excellent results, and without serious complications Ecchymosis was present on a few occasions, but cleared easily with no sequelae

Using sterile technique, we instilled 3 to 4 cc of 1 or 2 per cent novocain into the base of each corpus cavernosum with a No 22 needle and syringe Anesthesia is observed in 5 to 10 minutes Twenty-five to fifty milligrams of medication is injected through a No 18 needle with a 10 cc Luer-Lok syringe (The medication is almost impossible to inject through a smaller needle) Figure 3 clearly shows the large, rounded plunger-end of the medication syringe This and the finger holders are most important for forcible injection of the medication These plaques are usually very difficult to inject initially, however, the lateral margins are easier for the instillation of the drug Care should be taken to get all of the medication into the plaque or chordee One or two injections per week produce the best results A 2 by 8 gauze is firmly applied around the organ for ½ hours to help prevent bleeding Coitus is not desirable for 24 hours

DISCUSSION

The injection of either hydrocortisone or meticortelone in the treatment of Peyronie's disease has been of value Although it has only helped 30 per cent of the curvatures, it has relieved 61 per cent of pain in our 13 cases An average of 6–10 injections of 25 mg each of either hydrocortisone or meticortelone was necessary before any significant changes could be noted in the cases where changes did occur The optimal effect was reached between 15–20 injections The variations were attributable to the degree of fibrosis, extent of the lesions, whether calcium was present or not, involvement of the corpora cavernosa, and the skill of the operator in getting all of the medication into the plaque The latter is important, as no results may be expected without the proper injection of the medication The direction of the curvature could be altered at times with the site of the injection, a factor which should be utilized in the planning of the injections The best results were observed generally in those patients with a single noncalcified nodule The exception to this was seen in case 3 (table 10) which had x-ray evidence of calcium It is important to note that the duration of the plaque in the responsive cases was only for 8 months prior to treatment, while in the failure cases symptoms were present for 17 months When chordee was found or the corpora cavernosa were involved, very little improvement was generally seen

Steroidal injection for Peyronie's disease is a safe and easy method which can be used with facility in an office or out patient department On completion of his cases treated with steroid injections, Teasley asked his patients, "If you had known beforehand the results you have obtained now, would you repeat the treatments?" The answer in each case was ' Yes " Our patients were asked the same question and they also replied in the affirmative

SUMMARY

Until the underlying etiology is more clearly understood, the treatment of Peyronie's disease will remain varied The local injection of either meticortelone or hydrocortisone is an adjunct in the therapy of this condition, but as yet is not the final answer A larger sequence of cases is needed to enable us to ascertain more clearly its proper status

Thanks are extended to the following Schering Corporation for the meticortelone, Charles Pfizer & Co for the hydrocortisone, and the Ideal Pressure-Lock Syringes Co of East Rutherford, N J for constructing the rounded head plunger syringe, which was made especially for our use in this work Thanks to Dr Ralph Veenema for his guidance and assistance

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COLD ABSCESS OF THE PENIS SECONDARY TO RENAL TUBERCULOSIS

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Tuberculous infection of the penile urethra secondary to disease elsewhere in the genitourinary tract is a relatively uncommon condition. Cold abscess formation following such infection must be even more rare and very few cases have been reported. The following case would appear to be unique, as far as can be ascertained, in that a cold abscess of the penis was the sole presenting manifestation of an underlying renal tuberculous infection.

CASE REPORT

A man aged 23 years was first seen January 28, 1954 with a swelling which had been present on the ventral aspect of his penis for a year and was increasing in size. He had had no pain and no symptoms referable to his urinary or other systems. There was no relevant past or family history. He appeared well on examination, the only abnormal findings being referable to the penile swelling, which was 1 cm. in diameter, cystic, not tender and situated on the ventral surface of the penis, just proximal to the frenum. A diagnosis of dermoid cyst was made. On admission to the hospital 10 months later it was noticed that there was a small sinus over the swelling, but no discharge had been noticed or could be expressed from it.

On November 11 excision of the cystic swelling, which was found to be very close to the urethra, was accomplished. The pathological report was as follows:

"Ellipse of skin with a small sinus in the centre which goes through a mass of connective tissue. The cut surface shows congestion and some orange-brown pigmentation. Microscopic appearances are those of active tuberculosis. Acid-alcohol fast bacilli are present."

The wound healed but subsequently broke down and discharged. Further healing was followed by recurrence of the swelling. He was readmitted to the hospital February 11, 1955, the swelling at this time being approximately 1 cm. in diameter. Examination of the abdomen, testes, epididymides and seminal vesicles showed no abnormality. Early morning specimens of urine showed tubercle bacilli, and this finding was confirmed by culture of the organism. Pyelography showed that the left kidney was normal. There was calcification in the renal area on the right and cavitation in the lower pole of the right kidney with hydronephrosis and hydroureter. A chest x-ray was normal. Cystoscopy showed a reddened bladder with small tubercles in the mucosa. Chemotherapy with streptomycin, isoniazid and PAS was instituted for 3 months. The sinus over the penile swelling closed and remained healed, and the swelling itself gradually resolved.

The patient was readmitted February 6, 1956. Cystoscopy showed a red edematous area around the right ureteric orifice. A retrograde pyelogram con-

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firmed the previous findings and showed a stricture at the lower end of the right ureter On February 24 reimplantation of the right ureter into bladder was accomplished Convalescence was satisfactory apart from hematuria amounting to clot retention

On April 13 a right lower pole partial nephrectomy was performed Convalescence was uneventful The pathological report was as follows "Pole of a kidney It incorporates a dilated calyx the mucosa of which is thick and inflamed and in it is a mass of 'gravel' On the surface are multiple tubercles and on cutting these are seen to extend throughout a large part of the cortex and medulla Sections show chronic active tuberculosis "

The swelling on his penis has subsided and remained healed Urine specimens show no pus or tubercle bacilli An excretory urogram shows good function and a postoperative cystoscopy shows no evidence of inflammation in the bladder The patient continues well and has no urinary symptoms

DISCUSSION

Tuberculous involvement of the urethra is uncommon and usually occurs in the florid stage of genitourinary tuberculosis The bladder, prostate and epididymides are particularly likely to be grossly infected and stricture formation may follow the urethritis (Kilburn, Rochat) Nesbit records such a case in which ureteric transplantation became necessary to relieve the obstruction Blanc has reported a cold abscess, 2–3 cm in diameter on the ventral surface of the penis in a patient who already had gross tuberculous cystitis and epididymitis with sinus formation A further case recorded by Naggiar occurred after a nephrectomy for tuberculosis carried out the previous year In the present case the cold abscess was the presenting feature of the condition, and there were no urinary symptoms at any time to indicate the presence of an underlying kidney lesion It is considered that the abscess developed secondarily to a microscopic focus of tuberculous infection in the urethra

CONCLUSION

A case is presented in which a cystic swelling of the penis formed the presenting manifestation of a tuberculous infection of the kidney The nature of the swelling was only established after excision The literature is briefly reviewed

We would like to thank Mr T W Mimpriss for permission to report this case which was treated under his care

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CALCIUM PHOSPHATE SOLUBILITY IN URINE

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Since calcium phosphate is the commonest major component of renal calculi, accurate knowledge concerning the factors affecting its solubility in urine is of utmost importance in the prophylaxis and medical management of patients with calculus disease Although considerable qualitative data have been accumulated regarding calcium metabolism and changes in the urinary excretion of calcium and phosphorus in various disease states, accurate quantitative data regarding the solubility of calcium phosphate in urine are lacking in the medical literature

Largely due to the writings of Lichtwitz and Meyer, urine is generally considered to be supersaturated with calcium phosphate In 1909, 1910, and 1911 Lichtwitz observed that colloidal substances derived from urine exerted a protective effect in colloidal gold solutions In 1914 Lichtwitz observed that the concentrations of calculus-forming salts in urine were apparently greater than their solubilities in pure aqueous solution at 18°C On the basis of these observations, he concluded that urine was supersaturated, and advanced the hypothesis that protective colloids were responsible for this phenomenon Lichtwitz's hypothesis has gained general acceptance and has recently been used to substantiate a proposed treatment for nephrolithiasis

A review of Lichtwitz's original articles indicates, however, that his solubility data were quite inadequate judged by modern standards In any case, a comparison of solubility in urine to that in pure watery solution is meaningless Furthermore, later investigators, including Ascoli, Newcomb, Kohler, Goldberg, and Sisk and Toenhart, were unable to demonstrate that urinary colloids exerted any protective effect toward the common calculus-forming components Ferguson, in 1938, reported that urine from patients with calculus disease showed a greater protective effect toward colloidal gold suspensions than did normal urine More recently, Boyce, Garvey, and Norfleet, in a careful study, found that neither urinary colloids nor hyaluronidase exerted any protective effect in urines made turbid by the addition of sodium hydroxide

Meyer, in 1929, made an attempt to apply the solubility product principle to urinary salts Using average known concentrations of urinary salts and average cation strengths present in urine, he calculated a series of hypothetical ion products and solubility products His tables showing apparent supersaturation of urine have been widely reproduced and have served to increase the general acceptance of Lichtwitz's postulate Unfortunately, Meyer's work is of little value In the case of calcium phosphate, there are at least four fundamental variables, each of which may vary without relation to the others even in normal physiological states Since Meyer's values were purely hypothetical and not

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Aided by a grant from the National Foundation for Infantile Paralysis

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A review of Lichtwitz's original articles indicates, however, that his solubility data were quite inadequate judged by modern standards. In any case, a comparison of solubility in urine to that in pure watery solution is meaningless. Furthermore, later investigators, including Ascoli, Newcomb, Kohler, Goldberg, and Sisk and Toenhart, were unable to demonstrate that urinary colloids exerted any protective effect toward the common calculus-forming components. Ferguson, in 1938, reported that urine from patients with calculus disease showed a greater protective effect toward colloidal gold suspensions than did normal urine. More recently, Boyce, Garvey, and Norfleet, in a careful study, found that neither urinary colloids nor hyaluronidase exerted any protective effect in urines made turbid by the addition of sodium hydroxide.

Meyer, in 1929, made an attempt to apply the solubility product principle to urinary salts. Using average known concentrations of urinary salts and average cation strengths present in urine, he calculated a series of hypothetical ion products and solubility products. His tables showing apparent supersaturation of urine have been widely reproduced and have served to increase the general acceptance of Lichtwitz's postulate. Unfortunately, Meyer's work is of little value. In the case of calcium phosphate, there are at least four fundamental variables, each of which may vary without relation to the others even in normal physiological states. Since Meyer's values were purely hypothetical and not

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derived from quantitative measurements of concentrations of the salts concerned in individual urine specimens, they do not represent true values which may occur in either normal or pathological states. It should be noted that Meyer did not represent his calculated values to be other than theoretical.

To summarize then, there are no data in the literature from which any conclusions can be drawn regarding the degree of saturation of urine with calcium phosphate. It is clear that urinary colloids exert no significant protective effect.

With the foregoing in mind, the present study was undertaken in order to ascertain whether normal urine is supersaturated or undersaturated with calcium phosphate.

It has long been known that solubility of calcium phosphate in an aqueous solution depends upon three variables: 1) the hydrogen ion concentration, 2) the calcium ion concentration, and 3) the total inorganic phosphate concentration. More recently, the concept of "ionic strength"* developed by Lewis and Randall and others, has added a fourth variable. This concept was applied by Holt, LaMer, and Chown to a study of the influence of other salts on the solubility of calcium phosphate in salt solutions and serum. They showed that the presence of sodium chloride and other ions, such as magnesium, markedly increased the solubility of calcium phosphate. Sendroy and Hastings, studying the same problem, subsequently related the three dissociation constants of phosphoric acid to the ionic strength as follows:

$$pK_1' = 2.11 - 0.5\sqrt{\mu}$$

$$pK_2' = 7.15 - 1.25\sqrt{\mu}$$

$$pK_3' = 12.66 - 2.25\sqrt{\mu}$$

This relationship is of considerable importance since the concentration of $H_2PO_4^-$, $HPO_4^=$, and $PO_4^{\equiv}$ ions cannot be determined directly, but must be derived from calculations involving these constants. In addition to the four fundamental variables listed above, urine contains many organic substances including citric acid which may increase the solubility of calcium phosphate by the formation of soluble complexes.

METHOD

A. Twenty-four hour urine specimens were analyzed for 1) pH, 2) calcium concentration, 3) inorganic phosphorus concentration, and 4) ionic strength. In order to calculate the ionic strength, the concentrations of Na, K, NH_4, Cl, and SO_4 were determined.

B. 10.0 ml of 1N NaOH were added to a 200 ml aliquot of each urine specimen in a tightly stoppered flask and incubated at 38° for one week with daily shaking. The precipitate in each specimen was then removed by filtration through retentive paper, and the pH, concentration of calcium, concentration of inorganic phosphorus, and total ionic strength were redetermined in the filtrate.

C. ($H_2PO_4^-$), ($HPO_4^=$), and ($PO_4^{\equiv}$) were calculated using the equations of Sendroy and Hastings.

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* The ionic strength (μ) is defined as one half the sum of the molar concentrations of each ion multiplied by the square of its valence.

D. The ion product $(Ca^{++})^3(PO_4^{\equiv})^2$ in the original untreated urine was then calculated from the above data.

The ion product $(Ca^{++})^3(PO_4^{\equiv})^2$ in the urine after the addition of NaOH and incubation was similarly calculated.

The addition of sodium hydroxide to urine results in an increase in pH of the solution, and a minor change in ionic strength which has been considered in the calculations. The net effect is to increase the concentration of $(PO_4^{\equiv})$. This has the advantage of introducing only one variable factor, and does not exclude the effect of citrate or other organic acids.

ANALYTICAL METHOD

Urine was collected under oil for 24-hour periods from normal, healthy adults who were on unrestricted diet and fluid intake, and engaged in moderate physical activity. Toluene was used as a preservative. Within one to two hours after termination of the collection period, the pH was determined at 38°, using a Beckman model G pH meter. Sodium and potassium were determined directly on dilute urine by flame photometry. Ammonium was determined by the method of Van Slyke and Cullen with modifications as described by Hawk, Oser, and Summerson. Chloride was determined by the Volhard Arnold method, as modified and described by Hawk, Oser, and Summerson. Inorganic sulfate was determined by the method of Folin. Inorganic phosphate was determined by the method of Fiske and Subbarow. Calcium and magnesium were determined by a modification of the method of Michaels et al. as follows: To 25.0 ml. of urine in a 50 cc conical bottomed centrifuge tube were added 5 cc of 25 per cent solution of $(NH_4)_2HPO_4$ followed by the addition of excess concentrated NH_4OH. After standing overnight, the precipitate was separated by centrifuging and decanting. The precipitate and tube were washed twice with 5 per cent NH_4OH. The precipitate was dissolved in a small amount of 1–4 HCl. Calcium was then precipitated as oxalate at a pH of approximately 5.0 and allowed to stand overnight. The precipitate was centrifuged and washed twice with Sendroy's alcohol-ether wash. Calcium was then determined by conventional permanganate titration using 0.1 normal potassium permanganate. To the supernatant and washings were added 1 cc of 25 per cent $(NH_4)_2HPO_4$ and excess concentrated NH_4OH. After standing overnight, the precipitate was centrifuged and washed with ammoniated alcohol wash, redissolved in dilute HCl and magnesium was determined as phosphate.

Results of the analyses are tabulated in table 1, with concentrations expressed as Mols per liter.

CALCULATIONS

1) Ionic strength (μ). The ionic strength of each urine specimen was calculated by multiplying the molar concentration of each ion by the square of its valence, adding these values and dividing by two. Undetermined anions were considered to be univalent. Initially, phosphate was considered to be entirely $H_2PO_4^-$. After an approximate $HPO_4^=$ concentration was calculated, this value was included in a recalculation of ionic strength and $(HPO_4^=)$ was recalculated. In

TABLE 1*

Specimen	K D	J H	H H	R M	R S	J S	J E
Volume	1560	430	2040	2170	1454	2505	2145
Specific gravity	1 021	1 034	1 014	1 018	1 018	1 013	1 013
pH (1)	6 03	5 61	6 55	5 96	6 47	6 34	6 31
pH (2)	8 70	8 55	7 78	7 66	8 44	8 37	8 15
Ca (1)	0 00580	0 00462	0 00208	0 00323	0 00124	0 00235	0 00192
Ca (2)	0 000900	0 000128	0 000455	0 000890	0 000133	0 0000728	0 000326
P (1)	0 0295	0 0450	0 0174	0 0210	0 0175	0 0175	0 0143
P (2)	0 0207	0 0350	0 0143	0 0157	0 0142	0 0134	0 0123
Ionic strength (1)	0 252	0 392	0 160	0 244	0 247	0 179	0 175
Ionic strength (2)	0 440	0 670	0 203	0 284	0 262	0 198	0 199
$PO_4^{\equiv}$ (1)	2 27 $\times 10^{-8}$	1 43 $\times 10^{-8}$	4 75 $\times 10^{-8}$	1 14 $\times 10^{-8}$	6 91 $\times 10^{-8}$	2 62 $\times 10^{-8}$	1 82 $\times 10^{-8}$
$PO_4^{\equiv}$ (2)	7 02 $\times 10^{-5}$	1 88 $\times 10^{-4}$	1 85 $\times 10^{-6}$	2 33 $\times 10^{-6}$	1 21 $\times 10^{-5}$	6 83 $\times 10^{-6}$	3 74 $\times 10^{-6}$

* Concentrations expressed as mols per liter
(1) refers to value in original urine
(2) refers to value in urine after addition of sodium hydroxide

TABLE 2*

Specimen	K D	J H	H H	R M	R. S	J S	J E
Ion Product (1) $(Ca^{++})^3(PO_4^{\equiv})^2$	1 00 $\times 10^{-22}$	2 02 $\times 10^{-23}$	2 03 $\times 10^{-23}$	4 38 $\times 10^{-21}$	9 10 $\times 10^{-21}$	8 90 $\times 10^{-21}$	2 34 $\times 10^{-21}$
Ion Product (2) $Ca^{++})^3(PO_4^{\equiv})^2$	3 13 $\times 10^{-18}$	7 41 $\times 10^{-20}$	3 22 $\times 10^{-22}$	3 38 $\times 10^{-21}$	3 46 $\times 10^{-22}$	1 80 $\times 10^{-23}$	4 85 $\times 10^{-22}$
Factor of under-saturation	10^4	10^3	15	10^3	38	2 0	10^2

* (1) refers to value in original urine
(2) refers to value in urine after addition of sodium hydroxide

the calculation of ($PO_4^{\equiv}$), the final value for ionic strength was used This recalculation resulted in so little change in values as to be hardly significant

2) ($PO_4^{\equiv}$) *and* ($HPO_4^{=}$) In order to calculate the concentration of ($PO_4^{\equiv}$) and ($HPO_4^{=}$), the equations and dissociation constants of Sendroy and Hastings were used *

(1)
$$(PO_4^{\equiv}) = \frac{(P)K_1'K_2'K'}{(H^+)^2K_1' + (H^+)K_1'K_2'}$$

(2)
$$(HPO_4^{=}) = \frac{(P)(H^+)K_1'K_2'}{(H^+)^2K_1' + (H^+)K_1'K_2')}$$

(3)
$$pK_1' = 2\ 11 - 5\sqrt{\mu}$$

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* P = total inorganic phosphate, and $K_1'K_2'K_3'$ are the apparent dissociation constants of phosphoric acid

$$pK_2' = 7.15 - 1.25\sqrt{\mu}$$
$$pK_3' = 12.66 - 2.25\sqrt{\mu}$$

Although the dissociation constants of phosphoric acid have been studied by a number of workers since the report of Sendroy and Hastings, the difference in values is not significant for our purposes.

3) Ion products. The ion products $(Ca^{++})^3(PO_4^{\equiv})^2$ listed in table 2 were calculated by using the molar concentration of calcium as determined by analysis, and the concentrations of $(PO_4^{\equiv})$ which were calculated as indicated above. It should be noted that the value used for (Ca^{++}) is total (Ca).

DISCUSSION

By reference to table 2, it may be seen that the ion products labeled (2) are considerably larger than the ion products labeled (1). The factors of difference ranged from 2 to 10^4. This can only mean that these urines were undersaturated with $Ca_3(PO_4)_2$.

Calcium phosphate calculi are composed of hydroxyapatite. This substance does not exist in solution and in the solid state it probably represents a molecular rearrangement of $Ca_3(PO_4)_2$. Neither the dissociation constant of hydroxyapatite nor the solubility product of $Ca_3(PO_4)_2$ in urine is known at the present time. The ion products $(Ca)^3(PO_4)^2$ labeled (2) in this paper may or may not represent apparent solubility products of $Ca_3(PO_4)_2$. Further work is under way on this problem.

SUMMARY

Urine is generally considered to be supersaturated with calcium phosphate, a state made possible by the action of protective colloids.

A review of the literature has disclosed that there are no valid data to support either of the above assumptions.

Data obtained from a comprehensive quantitative chemical study of 24-hour urine specimens are presented in this paper. The results show that these urines were considerably undersaturated with tricalcium phosphate.

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THE EFFECT OF THERAPEUTIC DOSAGES OF NITROFURANTOIN (FURADANTIN) UPON SPERMATOGENESIS IN MAN*

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In 1944 Dodd and Stillman[1] found that addition of a 5-nitro group to the furan ring conferred marked bacteriostatic action to the derivative. As a result of these studies, a new compound was evolved—nitrofurazone (furacin)—which proved quite effective when used topically for chronically infected wounds and burns and later, for urethrotrigonitis. Thereafter, further experimentation produced a series of compounds including nitrofurantoin (furadantin) N-(5-nitro-2-furfurylidene)-1-amino-hydantoin—a yellow crystalline compound of better taste which darkens on exposure to light or alkali and which produces a higher urinary level than some other nitrofurans.

Several clinical studies[2, 3, 4] with furadantin have indicated its effectiveness as a urinary antibacterial agent and investigations in animals and men following orally administered doses revealed high concentrations (approximately 45 per cent) in the urine in the presence of low blood levels. Since recent observations by Nelson and Steinberger[5, 6] have shown that the nitrofurans including furadantin produce temporary spermatogenic arrest at the stage of the primary spermatocyte in the rat testis, the question arose as to the possible effect of these drugs in man. Testicular biopsies following furadantin treatment of small series of patients had previously been reported as normal by Carroll and Brennan[7] and Waisbren and Crowley[8] while Schmidt[9] found no variation in sperm counts. The present study was undertaken to evaluate more thoroughly the effects of therapeutic doses of furadantin on the human testis.

METHODS

A total of 36 young healthy white male volunteers between the ages of 19 and 35 were selected from university students and inmates of two nearby prisons. They were divided in three groups.

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THE EFFECT OF THERAPEUTIC DOSAGES OF NITROFURANTOIN (FURADANTIN) UPON SPERMATOGENESIS IN MAN*

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In 1944 Dodd and Stillman[1] found that addition of a 5-nitro group to the furan ring conferred marked bacteriostatic action to the derivative. As a result of these studies, a new compound was evolved—nitrofurazone (furacin)—which proved quite effective when used topically for chronically infected wounds and burns and later for urethrotrigonitis. Thereafter, further experimentation produced a series of compounds including nitrofurantoin (furadantin), N-(5-nitro-2-furfurylidene)-1-amino-hydantoin—a yellow, crystalline compound of bitter taste which darkens on exposure to light or alkali and which produces a higher urinary level than some other nitrofurans.

Several clinical studies[2, 3, 4] with furadantin have indicated its effectiveness as a urinary antibacterial agent and investigations in animals and men following orally administered doses, revealed high concentrations (approximately 45 per cent) in the urine in the presence of low blood levels. Since recent observations by Nelson and Steinberger[5, 6] have shown that the nitrofurans, including furadantin, produce temporary spermatogenic arrest at the stage of the primary spermatocyte in the rat testis, the question arose as to the possible effect of these drugs in man. Testicular biopsies following furadantin treatment of small series of patients had previously been reported as normal by Carroll and Brennan[7] and Waisbren and Crowley,[8] while Schmidt[9] found no variation in sperm counts. The present study was undertaken to evaluate more thoroughly the effects of therapeutic doses of furadantin on the human testis.

METHODS

A total of 36 young, healthy, white male volunteers, between the ages of 19 and 35, were selected from university students and inmates of two nearby prisons. They were divided in three groups.

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TABLE 1

Patient	Pretreatment Average Total Sperm Count	Furadantin Daily Dose in Mg For 2 Weeks	Total Sperm Count 1–4 Weeks After Beginning of Treatment	Total Sperm Count 5–8 Weeks After Beginning of Treatment	Total Sperm Count 9–12 Weeks After Beginning of Treatment	Total Sperm Count 1–2 Weeks After Beginning of Treatment	Additional Observations	Biopsy Findings
D K	320^{2}	600	270^{5}	202^{1}	295^{1}	402^{1}		No biopsy
M S	516	650	362^{7}	420^{3}	282^{2}	393^{4}		No biopsy
W D	302^{4}	400	388^{7}	330^{3}	302^{1}	356^{4}	Calculated dose = 700 tolerated—400	No biopsy
R W	201^{2}	600	185^{4}	—	360^{1}	264^{4}	Calculated dose = 850 tolerated—600	No biopsy
H W	45^{4}	750	85^{4}	117-	—	—		No biopsy
F B	238^{3}	500	440^{5}	310^{1}	—	—		No biopsy
N P	461^{4}	700	601^{3}	299	—	320-		No change in biopsies, Interval 4 weeks
W T	40^{1}	650	15^{1}	—	92	15^{1}		No change in biopsies Interval 2 weeks
G A	30^{1}	600	—	—	63^{1}	270^{4}		No change in biopsies Interval 2 weeks
M M	480^{1}	700	—	—	—	—		No change in biopsies Interval 2 weeks
L H	176^{1}	600	—	191^{2}	380^{1}	206^{1}		No change in biopsies 2 weeks interval
P K	213^{1}	650	—	37^{1}	—	—		No change in biopsies 2 weeks interval
W C	213	800	168^{1}	156^{1}	—	102^{1}		No change in biopsies 2 weeks interval
D A	195^{1}	80	556^{1}	294	—	355^{1}		No change in biopsies 2 weeks interval
J H	240^{1}	850	184^{1}	124^{1}	—	—		No change in biopsies 2 weeks interval
F A	263^{1}	700	195^{1}	—	—	269^{1}		No change in biopsies 2 weeks interval
D G	15^{1}	600	7.5^{1}	66^{1}	—	7.5^{1}		No change in biopsies 2 weeks interval
G R	873^{1}	700	214^{1}	—	—	—		No change in biopsies 2 weeks interval

* Superscript = Number of counts All sperm counts are given in millions

The reduced sperm production was apparent in reduction of the counts 4 to 13 weeks after the beginning of drug therapy One individual had a bilateral vasectomy at the time of the second biopsies consequently no subsequent semen samples were collected

5) No alteration in liquefaction time was observed in post-treatment semen

All members gave semen samples with a minimum continent period of 3 days before oral administration of the drug (The reliability of the continent period was better in the university students than in the prisoners) The usual semen examinations were done, including viability count with eosin-nigrosin stain All subjects were given furadantin, 10 mg per kg of body weight, orally in 4 divided doses daily In some cases the dosage was dropped to tolerance levels, as indicated in the tabulations Two groups of student volunteers were formed, one group of 11 students gave pre-treatment and post-treatment semen samples only, while in the other group of 6, semen samples as well as pre- and post-treatment testicular biopsies were obtained The interval between biopsies was 2 to 4 weeks with the majority in the 2 weeks' period In most instances, the biopsies were bilateral A third group of 19 prisoner volunteers had both semen analyses and biopsies Because of difficulties associated with obtaining dependable semen samples in these subjects, our principal interest in this group was centered on the effect of the drug on testicular histology

All biopsies were fixed in Bouin's solution and stained by trichrome aldehyde fuchsin, iron hemotoxylin-eosin, Masson, and periodic acid-Schiff procedures Testicular histology was interpreted by the senior author without knowledge of sperm counts Biopsies were made by the junior author and semen samples were examined in his laboratory employing standardized methods Sperm counts are given as total counts, since these are more representative of sperm producing capacity than counts in terms of cubic centimeters

RESULTS

1) Of the 36 individuals involved in the study, 18 showed no significant variations in the total sperm counts before and after furadantin therapy (table 1) Twelve individuals in this group had testicular biopsies before and after treatment None showed any histologic variation attributable to the drug

2) A slight decrease in total sperm counts was noted in 5 individuals (table 2) This was so slight, however, that if the expected variability in counts is taken into account, it is probable that no real inhibition occurred It is significant that no change was discernible in the testicular biopsies

3) In 5 cases a depression of the total sperm counts was noted in the period 5 to 8 weeks following the initiation of treatment Recovery was usually noted in the 9 to 12 week period similarly calculated No histologic evidence of testicular suppression was noted in the biopsies of the five individuals concerned (table 3) Case D N is not quite in line with the remaining four in the group The single high initial count was not in agreement with the histologic state of the testes and may be a technical error since the subsequent counts did fall in line with the biopsies

4) There were 8 individuals who showed decreased sperm counts, 7 of these showing histologic evidence of drug effect (table 4) This effect was manifested by definite tendency toward arrest and sperm production was decreased, but by no means halted completely Polynucleated cells were increased in some instances

TABLE 1

Patient	Pretreatment Average* Total Sperm Count	Furadantin Daily Dose in Mg For 2 Weeks	Total Sperm Count, 1-4 Weeks After Beginning of Treatment	Total Sperm Count 5-8 Weeks After Beginning of Treatment	Total Sperm Count 9-12 Weeks After Beginning of Treatment	Total Sperm Count 13-32 Weeks After Beginning of Treatment	Additional Observations	Biopsy Findings
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F B	238^{3}	500	440^{5}	310^{1}	—	—		No biopsy
N P	461^{4}	700	601^{3}	299^{7}	—	320		No change in biopsies, Interval 4 weeks
W T	40^{1}	650	15^{1}	—	92	15^{1}		No change in biopsies Interval 2 weeks
G A	30^{1}	600	—	—	63^{1}	279^{4}		No change in biopsies Interval 2 weeks
M M	480^{1}	700	—	—	—	—		No change in biopsies, Interval 2 weeks
L H	176^{1}	600	—	191^{2}	380^{1}	206^{1}		No change in biopsies 2 weeks interval
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J H	240^{1}	850	184^{1}	124^{1}	—	—		No change in biopsies 2 weeks interval
F A	263^{1}	700	195^{1}	—	—	269^{1}		No change in biopsies 2 weeks interval
D G	15^{1}	600	$7\ 5^{1}$	66^{1}	—	$7\ 5^{1}$		No change in biopsies 2 weeks interval
G R	873^{1}	700	214^{1}	—	—	—		No change in biopsies 2 weeks interval

* Superscript = Number of counts All sperm counts are given in millions

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4) There were 8 individuals who showed decreased sperm counts, 7 of these showing histologic evidence of drug effect (table 4) This effect was manifested by definite tendency toward arrest and sperm production was decreased, but by no means halted completely Polynucleated cells were increased in some instances

TABLE 4

Patient	Pre treatment Average Total Sperm Count	Furadantin Daily Dose in Mg for 2 weeks	Total Sperm Count 1–4 Weeks After Beginning of Treatment	Total Sperm Count 5–8 Weeks After Beginning of Treatment	Total Sperm Count 9–12 Weeks After Beginning of Treatment	Total Sperm Count 13–32 Weeks After Beginning of Treatment	Additional Observations	Biopsy Findings
G N	129.5^{2}	700	194^{4}	24^{6}	—	80^{1}	Motility dropped from good to fair	Biopsy interval 4 weeks Perhaps a moderate degree of arrest has been caused with a moderate decline in sperm output
J R	21^{1}	600	—	—	—	—	Patient had vasectomy at second biopsy Effect on testis only planned observation	Spermatocytic arrest seems to be more evident than initially
S P	47^{1}	700	—	45	65^{1}	931^{2}		Initial biopsy histologically better than sperm count indicated Second biopsy (2 week interval) showed definite arrest at spermatocyte stage
S F	663^{1}	600	663^{1}	—	27^{2}	295^{1}		No significant change in biopsy Interval 2 weeks
L S	74^{1}	700	9^{1}	—	—	77^{1}		Definite tendency towards arrest Sperm production definitely less Interval 2 weeks
R H	191^{2}	500	63^{2}	—	—	—	Calculated dose = 950, Tolerated dose = 500	Slight tendency toward arrest with reduced sperm production
D K	432^{1}	800	119^{1}	—	—	52^{1}		Biopsy interval 2 weeks Moderate degree of arrest
A	490^{1}	750	238^{4}	57^{1}	60^{1}	228^{1}		Definite tendency toward arrest Biopsy 2 weeks interval

* Superscript = Number of counts All sperm counts are given in millions

6) Intolerance to the calculated dose of 10 mg per kg of body weight (slightly higher than the usual therapeutic amount) was manifested by headache, nausea, and at times vomiting These appeared in the student group, and were rarely reported in the prison group In the latter group, each volunteer took the drug in the presence of a guard

TABLE 2

Patient	Pretreatment Average Total Sperm Count*	Furadantin Daily Dose in Mg For 2 Weeks	Total Sperm Count 1–4 Weeks After Beginning of Treatment*	Total Sperm Count 5–8 Weeks After Beginning of Treatment	Total Sperm Count 9–12 Weeks After Beginning of Treatment	Total Sperm Count 13–32 Weeks After Beginning of Treatment	Additional Observations	Biopsy Findings
W H	356^{2}	850	503	142^{1}	400^{1}	335^{6}		No change in biopsies
T K	21^{2}	900	6^{4}	15^{1}	15^{1}	15^{2}		No change in biopsies
N E	8.5^{2}	400	5^{5}	3^{1}	—	12.5^{1}	Calculated daily dose = 900 mg Tolerated = 400 mg	No change in biopsies
R B	230	400	160	261	—	—	Calculated daily dose = 800 mg Tolerated = 400 mg	No change in biopsies
E H	312^{2}	500	153^{6}	—	—	382^{1}	Calculated daily dose = 700 mg Tolerated = 500 mg	No change in biopsies

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Patient	Pretreatment Average Total Sperm Count*	Furadantin Daily Dose in Mg For 2 Weeks	Total Sperm Count 1–4 Weeks After Beginning of Treatment*	Total Sperm Count 5–8 Weeks After Beginning of Treatment	Total Sperm Count 9–12 Weeks After Beginning of Treatment	Total Sperm Count 13–32 Weeks After Beginning of Treatment	Additional Observations	Biopsy Findings
J V	687^{2}	600	532^{5}	331^{5}	432			No detectable change Interval 2 weeks
P H	180^{3}	400	209^{5}	19.4^{2}	140^{1}	—	Calculated daily dose = 850 mg Tolerated = 400 mg	No detectable change Interval 2 weeks
A F	492^{1}	600	287^{4}	103^{5}	—	—		No detectable change Interval 2 weeks
D N	820^{1}	600	32^{1}	—	66^{1}	15^{1}		No detectable change in biopsies, but original biopsy did not agree with high initial count
G J	29^{1}	850	—	27	8^{1}	5^{1}		No change in biopsies Interval 2 weeks

* Superscript = Number of counts All sperm counts are given in millions

samples, except in one case However, following ingestion of the drug, definite yellow coloration of the semen was noted in several cases, as previously reported by Trautner [10]

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[10] Trautner, K Hvorledes behandler de prostatitis Ugeskr laeger **116** 1535, 1954

TABLE 4

Patient	Pre-treatment Average Total Sperm Count*	Furadantin Daily Dose in Mg for 2 weeks	Total Sperm Count 1–4 Weeks After Beginning of Treatment*	Total Sperm Count 5–8 Weeks After Beginning of Treatment	Total Sperm Count 9–12 Weeks After Beginning of Treatment	Total Sperm Count 13–32 Weeks After Beginning of Treatment	Additional Observations	Biopsy Findings
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G J	29^{1}	850	—	27^{2}	8^{1}	5^{1}		No change in biopsies Interval 2 weeks

* Superscript = Number of counts All sperm counts are given in millions

samples, except in one case However, following ingestion of the drug, definite yellow coloration of the semen was noted in several cases, as previously reported by Trautner [10] motility where the counts were less than 75 millions The evidence was sufficient to lead us to suspect that these 10 individuals were probably relatively infertile at best There was good agreement between the histologic aspect and sperm microscopic findings in this group

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[10] Trautner, K Hvorledes behandler de prostatitis Ugeskr laeger, **116** 1535 1954

In 14 cases of the furadantin series, the pre- and post-treatment biopsies were analyzed by the Chalkley method These biopsies had been selected from the 27 cases listed in tables 1, 2 and 3, where routine histologic studies had failed to reveal evidence of spermatogenic arrest Details of the findings are being published in a separate paper (Roosen-Runge, Marberger, and Nelson[11]) At this time it is sufficient to say that the method as applied provides a means of analyzing quantitatively the structures of the testis It has definite defects in that it offers only a percentage count of the structural elements of the testicular sample It does not, for example, indicate whether the germinal cells are attached to the Sertoli cells or sloughed into the tubular lumina, and it does not provide information as to the *total* cellular constituents of the testis It does, however, furnish a method of quantitating the testicular elements and permits objective evaluation of the spermatogenic process in terms of its several stages

As applied to the cases in question, the method indicated that the administration of furadantin for 14 days at therapeutic levels had no significant effect upon spermatogenesis Thus, the junior author has continued to employ the drugs in treating urinary tract infections

Yellowish coloration of the semen samples was due presumably to furadantin or its breakdown products entering the seminal fluid through structures supplying that medium Studies are underway to determine if furadantin is concentrated in the prostatic fluid

It was of interest to observe the lower incidence of intolerance to the drug in the less knowledgeable group of prisoner volunteers The students, for the most part juniors in the medical school, were more likely to anticipate manifestations of intolerance Although definite proof is lacking, one gains the impression that a psychogenic influence was in part responsible for the lower tolerance in the student volunteers

SUMMARY

Furadantin given perorally in doses approximately 10 mg per kg daily to young healthy white males may in certain unpredictable instances produce slight to moderate temporary spermatogenic arrest Of 36 volunteers who took the compound for 14 days, 23 showed no significant change in sperm counts or testicular biopsies In 13 cases a temporary decrease in the sperm counts was noted but no changes could be detected in the testicular biopsies of 6 of these individuals The incidence of arrest is even less likely to occur with the lower clinical doses now in current use, and there seems little reason to fear that use of the drug in treatment of urinary tract infections will cause significant interference with fertility

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[11] Roosen-Runge, E , Nelson, W O and Marberger, E Quantitative investigations on human testicular biopsies II Volume proportions of tissue components in biopsies from abnormal human testicles Fertility and Sterility, in press

COMMENTS

Since it is likely that the spermatozoa which appear in the ejaculate pass through the stages from primary spermatocyte to spermatozoon and travel from the testis to the ampullary region in approximately four weeks, any effect on sperm production should be noted in the semen samples collected 3 weeks or more after initial administration of the drug This would depend, of course, upon the stage of spermatogenesis which may be affected If, as is known to occur in the rat, the primary spermatocytes are arrested from further development, the elapsed time would be approximately four weeks Where definite suppression was noted in the seminal specimens, it occurred most frequently in the 5 to 8 weeks' period following the initial dose of drug A detectable recovery to or near pre-treatment levels in such cases was observed usually in the 9 to 32 weeks' period after beginning of treatment

Inasmuch as this study was concerned primarily with the effect of therapeutic levels of furadantin upon spermatogenesis, no attempt was made to employ higher doses On the basis of experience from studies with rats, the amounts used in this investigation were considerably less than would be required to arrest spermatogenesis completely and uniformly As has been noted in the discussion of the results, most of the individuals observed in this study showed no evidence of spermatogenic disturbance Where interference was noted, it appeared incomplete and transient The few instances in which post-treatment sperm counts had not attained levels comparable to those seen before treatment are not regarded as significant since the number of counts in these cases were not adequate As has been noted earlier, the inmates of penal institutions proved to be somewhat less than reliable subjects

It is worth noting that of the 25 cases in which pre- and post-treatment biopsies were obtained, the pre-treatment biopsies of only 13 were regarded as histologically normal Of the 25 cases, 6 were medical students, 19 were inmates of penal institutions In the student group, 3 were normal, in the prisoners, 10 were within the range of normality Since these cases may be regarded as having been random selections, it seems evident that the testes of presumably normal men may show a very wide range of histologic appearance and may in many instances be substandard

Much the same situation holds for the pre-treatment findings on seminal specimens Although in some instances, the number of counts obtained before treatment was not adequate to assure us that they were representative of the individuals' seminal function, the followup specimens were in almost every case so similar that they may be regarded as confirming the initial samples

If the 36 cases in which seminal specimens were obtained are divided into groups on the basis of *total* sperm counts, it may be seen that 10 showed counts of more than 400 millions, 11 falling between 201 and 400 millions, 5 between 75 and 200 millions, and 10 less than 75 millions In general the percentage and quality of sperm motility were in good agreement with the total count, i e , good sperm motility was noted in the case of total counts over 75 millions and poor motility where the counts were less than 75 millions The evidence was sufficient to lead us to suspect that these 10 individuals were probably relatively infertile at best There was good agreement between the histologic aspect and sperm microscopic findings in this group

In 14 cases of the furadantin series, the pre- and post-treatment biopsies were analyzed by the Chalkley method These biopsies had been selected from the 27 cases listed in tables 1, 2 and 3, where routine histologic studies had failed to reveal evidence of spermatogenic arrest Details of the findings are being published in a separate paper (Roosen-Runge, Marberger, and Nelson[11]) At this time it is sufficient to say that the method as applied provides a means of analyzing quantitatively the structures of the testis It has definite defects in that it offers only a percentage count of the structural elements of the testicular sample It does not, for example, indicate whether the germinal cells are attached to the Sertoli cells or sloughed into the tubular lumina, and it does not provide information as to the *total* cellular constituents of the testis It does, however, furnish a method of quantitating the testicular elements and permits objective evaluation of the spermatogenic process in terms of its several stages

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THE PATHOGENESIS OF IDIOPATHIC HYDROCELE AND A SIMPLE OPERATIVE TECHNIQUE

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The vaginal sac around the testis normally contains a few drops of clear, serous fluid, any appreciable increase in amount is called hydrocele

Idiopathic hydrocele develops slowly, without evidence of pre-existing disease of the urogenital tract However, it has been thought that the etiology is based upon some undisclosed or healed infectious process

Only men and arthropoid apes possess a tunica vaginalis which does not communicate with the peritoneal cavity The common laboratory animals have a patent vaginal process Therefore, experimental work on hydrocele has been impossible

PATHOGENESIS

The lymphatics of the testicle, epididymis and tunica vaginalis pass upward within the spermatic cord and enter the preaortic lymph nodes There is no lymph drainage from these structures to the inguinal nodes, because these are originally intra-abdominal structures and retain their original intra-abdominal connections This fact is also important as regards metastases of malignant diseases of the testicles and of the vaginal sac

The other outer coverings of the testicles are continuous with the neighboring tissues, and the lymphatics of these layers drain into the inguinal nodes These two entirely different courses of the lymphatics are important

In normal men the parietal layer of the tunica vaginalis propria has well defined channels of lymphatic system The studies by Rinker and Allen have demonstrated this fact quite clearly In idiopathic hydrocele these chains of lymphatics are permanently damaged in most parts of the membrane

Huggins and Entz reported their experiments on quantitative absorption of phenolsulfonphthalein of normal men with and without hydrocele They found that absorption from the tunica vaginalis testis was much more slow than from any of the serous cavities and that the absorption of dyes in hydrocele was much less

We also studied the time of output of indigo carmine from the kidney injected into the vaginal sac with and without hydrocele The results were the same

Both the aforementioned anatomic and histologic characters and experiments show that there is a lymphatic defect and consequently an insufficiency in reabsorption Thus the pathogenesis of hydrocele may be explained as follows There is evidently a constant changing of the fluid in all such serous cavities, with a balance between secretion and absorption There is an overproduction of fluid in acute form, and an impairment of reabsorption due to insufficiency of the lym-

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phatics in chronic hydroceles Shortly, in idiopathic hydrocele, the reabsorption is not enough to keep pace with secretion

DISCUSSION

Now the principles of treatment of the hydrocele should be considered as follows 1) to stop or decrease the secretion, 2) to improve or increase the reabsorption, 3) or to take advantage of both possibilities

Several methods of operations on hydrocele have been described These are total excision, partial excision and eversion or eversion only of the vaginal sac But these procedures have most troublesome sequelae such as hemorrhage, induration, infection The patient comes with a soft mass in the scrotum and leaves the hospital with a hard swelling, which eventually absorbs itself, but in the meantime the mass causes both patient and surgeon considerable anxiety

So far there has been no exact explanation as to how these radical procedures cure the hydrocele It is believed that the excision of the sac results in the cessation of the secretion, and that the eversion causes adhesions of the secretion surface to the outer layers But all these views are not correct, because when these methods are used secretion still continues from the visceral layer and also parietal layer, if present, and adhesions do not occur The real explanation is as follows

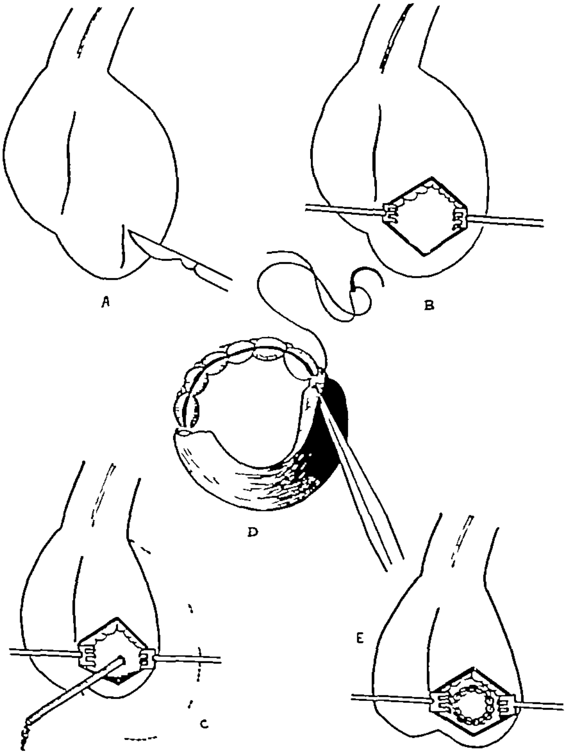

FIG 1

Either excision or eversion enables passage of the liquid, which is confined and unabsorbed in the sac, in the outer layers Thus the liquid is absorbed from the lymphatics of the outer layers and transported to the inguinal lymph nodes

According to this explanation, there is no need to use the aforementioned methods which usually lead to complications We can cure the hydrocele with a simple and easy procedure, now to be described

We thought that if we maintained a permanent window on the outer wall of the sac we could obtain the same excellent results without great damage Our method is as follows (fig 1)

After the scrotum has been properly prepared and draped, a 3 to 4 cm long incision is made on the anterior surface or preferably on the median line It would be better to make this incision near the bottom The loose areolar tissues are separated by retractors When the inner coverings are exposed the sac is opened and the liquid suctioned, then the opening widened The ridges are folded on themselves and sutured with a thin catgut, and thus a permanent window of 3-cm diameter is formed Hereafter the skin is sutured Thus the secreted fluid *passes through the window into the outer layers and is absorbed*

We call this procedure "window or fenestration method" We used it on 70 patients with success The only complication was swelling of the testicle We believe that it is due to immediate decompression of the liquid Therefore, it would be advisable to withdraw nearly half of the liquid during the days before operation

SUMMARY

The pathogenesis of the hydrocele is reviewed The principles of its treatment are considered The mechanism of the manner in which radical procedures cure the hydrocele is explained A simple and easy operative method which we proved to be successful in 70 patients is described

Note The number of our operated cases reached 106 during proof-reading

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TERATOMA OF TESTIS IN AN INFANT

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A case of a malignant tumor of the testis in an infant 16 months of age is to be presented In a review of the literature it has been found that malignant tumors of the testes are quite rare in the early age group and no evidence of a similar case could be found The differential diagnosis and approach to therapy are presented

A 16-month-old, well developed white boy was admitted to St Francis Hospital, Evanston, Illinois with a diagnosis of a left scrotal mass The past history was that of painless swelling in the left scrotal compartment which was first noted by the mother 8 months prior to admission There was no history of trauma, pain, or induration in the scrotal wall The mass gradually increased in size Approximately eight weeks prior to admission, in that the mass could not be reduced, was nontender and some transillumination was possible, 10 cc clear fluid was aspirated The size of the scrotal mass was reduced somewhat However, the essential pathological process remained, namely, an enlarged left testis

On admission the physical examination was within normal limits except for the left scrotal compartment which revealed a mass the size of an almond, which was firm and did not transilluminate light There was no evidence of adenopathy or induration in the associated spermatic cord The blood count was within normal limits The urinalysis was normal A 24-hour urine study for Aschheim-Zondek level was negative A chest x-ray was normal and the excretory urogram revealed good function bilaterally with normal renal architecture and no evidence of deviation of the course of either ureter

The patient was taken to surgery on August 18, 1953 and the testis delivered through a scrotal incision The tunica vaginalis was opened and minimal free fluid was found The testis was found to be approximately four times its normal size After isolating the testis, the tunica albuginea was opened The parenchyma of the testis revealed hard, bony areas, hair, cystic cavitation and gelatinous degeneration Gross inspection suggested an adult teratoma of the testis The incision was elongated and the testis and associated spermatic cord were excised at the level of the internal inguinal ring On August 27, 1953, a left retroperitoneal lymph node dissection was done No positive nodes were found

Pathology report (Dr J W Henry) The tissue excised was that of a testis measuring 3 8 by 4 5 by 2 8 cm (fig 1, *A*) Histologic diagnosis was that of a teratoma of the left testis of the adult type All structures including nerve, mucus secreting, glandular tissues and bone were mature (fig 1, *B*) Tissue submitted following retroperitoneal node dissection revealed no evidence of lymphatic permeation by tumor

In a survey of 127 cases of teratoma of the testis, the age group was between 20 and 39 years The presenting complaints were those of a painless swelling in

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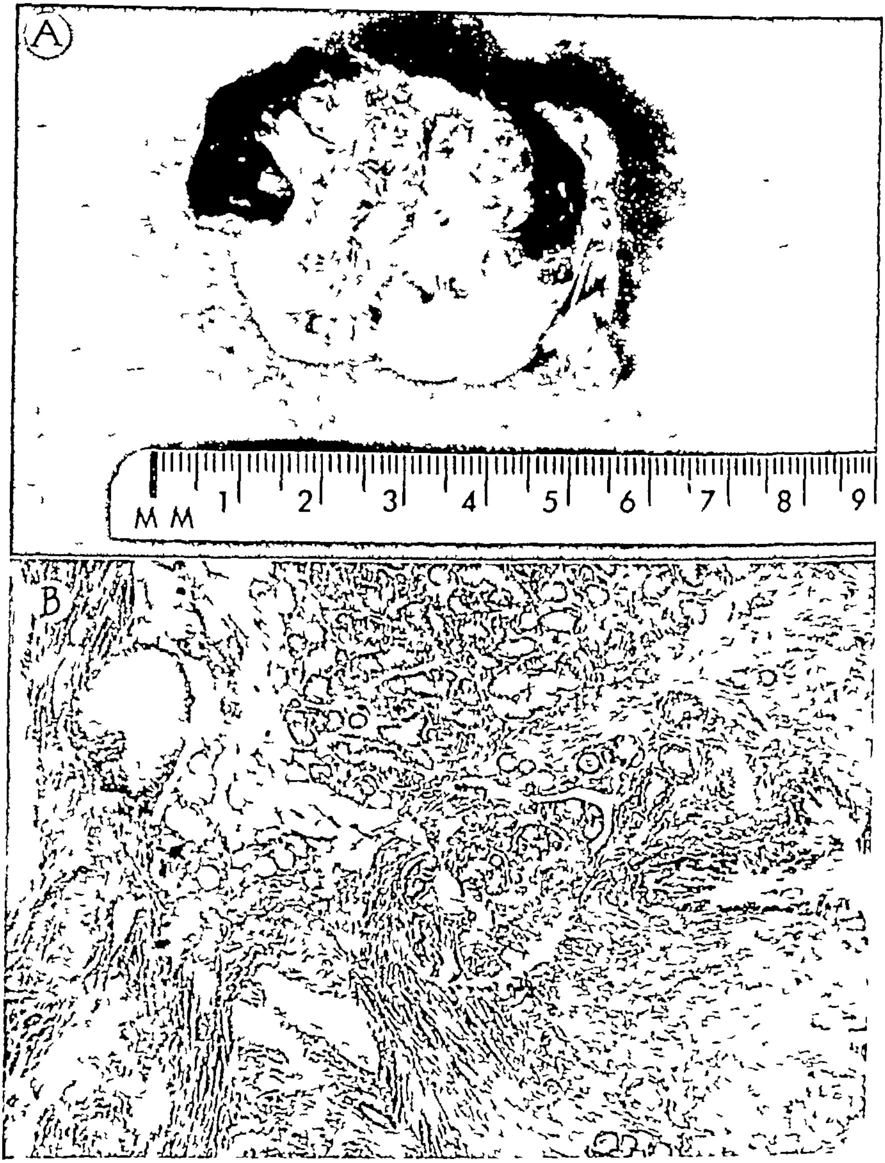

Fig 1 *A*, testis showing gross teratoid changes *B*, histological detail Note three basic germ layers

89 cases, a hydrocele in 11, and undescended testis in 4 Approximately 10 per cent of testis tumors in this group were associated in onset with hydrocele This would indicate the relatively high percentage of testis tumors with a presenting complaint of this type, and prove the necessity of a surgical exploration of a hydrocele of rapid onset and whenever transillumination is difficult or questionable It has also been found that 5 5 per cent of teratomas of the testis had chorioepitheliomatous elements Moore states that 5 per cent of patients with

adult teratomas of the testis will die from metastases from a malignant tumor which has the appearance of an embryonal carcinoma The primary tumor in this case is uniformly of the adult type despite numerous sections

The greatest incidence of teratoma is in the third decade, but a large number of cases also occur in the fourth decade The presence of chorionomatous elements in a teratoma indicates that it is a more primitive type Teratoid tumors may be either genital teratoid or extragenital and involve the retroperitoneal, mediastinal and sacrococcygeal areas as well as the pineal gland The extragenital teratoid tumors are more common in the younger age group and involvement of the genitals is more commonly seen as noted in the third and fourth decade In the case presented the teratoma was a primary genital tumor without any evidence of extragenital involvement The presence of a hydrocele made the initial diagnosis more difficult in view of the rarity of the tumor involved It is felt that this case emphasizes again the need for exploration of an explained hydrocele of rapid onset The possibility of a new growth in an infant must be considered when the patient's presenting complaint is that of a scrotal mass In terms of incidence, the probability would be that of a hernia or hydrocele

The patient has been followed for 3 years and has made a complete and uneventful recovery There is no evidence of metastatic lesions He has gained weight and has grown according to the usual patterns for his age His chest x-rays have been negative and he is now in apparent good health

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PRONE POSITION FOR TRANSURETHRAL PROCEDURES IN MALE PATIENTS

CHARLES H BEACH

Reginald Hancock[1] pointed out the feasibility and the advantages of the prone position in transurethral resection of anteriorly located vesical lesions in the female However, in the last sentence of his paper he says, "This position has not been applicable to the male patient "

The purpose of this brief report is to correct this impression It occurred to the author that a perineal urethrotomy should bypass the only impediment to employing this very ingenious new approach in the male (i e , the penile urethra with its limiting suspensory ligament) On June 19, 1956, this method was successfully employed in the resection of two grade 1 papillary carcinomas from the anterior wall This operation was done by the author at Highland Alameda County Hospital while a resident at that institution I was particularly impressed by the ease of the procedure utilizing Hancock's position, for 3 months earlier a prior resection in the same location in this same patient in the standard supine position had proved very arduous both to myself and an assistant who was pushing strenuously on an obese anterior abdominal wall

Many urologists, with good reason, will often forsake the resectoscope for suprapubic surgery in the treatment of bladder tumors on the dome The desire to excise a wide margin around the lesion is not the only reason for this It is well known that the resection of these tumors is more frequently associated with either extravasation on the one hand or incomplete resection on the other, as well as being more difficult technically This is particularly true of lesions located between 10 and 12 o'clock on the inner surface of the vesical neck

It is believed that more frequent usage of Hancock's prone position in both the male and female will popularize and increase the efficacy of the transurethral attack on bladder lesions located on the anterior wall

401 29th St , Oakland, Calif

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FIBRINOLYSIS FOLLOWING PROSTATIC SURGERY

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Fibrinolysis is a term coined and apparently first used by Dastre[1] in 1893 Although this phenomenon of aseptic breakdown of whole blood clots in vitro has been known for over a century, it has only been in the past few years that the possible significance of increased plasma proteolytic activity in vivo has been recognized The importance of fibrinolysis in the pathogenesis of some hemorrhagic diatheses has possibly been overlooked by earlier investigators because in its extreme form it occurs only rarely and with apparent irregularity That urologists should be aware of fibrinolysis is evident by the fact that at the Los Angeles County Hospital in the past year the urological service recognized 5 cases in 302 transurethral procedures as compared with three cases in approximately 3500 general surgical procedures

The terminology for the current concepts of the proteolytic enzyme system of plasma is not standardized in the literature Figure 1, proposed by Scott et al,[2] illustrates schematically the balanced enzyme system in plasma with delicate equilibrium between an active enzyme called plasmin (fibrinolysin) and its inhibitor called antiplasmin (antifibrinolysin) The precursor of plasmin (fibrinolysin) is termed plasminogen (profibrinolysin) Note that plasminogen and plasmin reside in the globulin fraction of the plasma and antiplasmin in the albumin fraction The activation in pathological conditions of this plasma enzyme system may cause a complete breakdown of the hemostatic mechanism with resultant severe bleeding manifestations termed by Stefanini[3] "fibrinolytic purpura" This hemorrhagic diathesis is probably due to enzymatic digestion not only of the fibrin clot but also of all other proteins involved in the process of blood coagulation It is evident since the enzyme system is not fastidious in its lytic activity that this system is proteolytic rather than just fibrinolytic Plasminemia is a term denoting an increased quantity of circulating plasmin

The exact details of the mechanism of abnormal plasma proteolytic activity are as yet undetermined From clinical and experimental studies it can be postulated that abnormal proteolytic activity may occur under a number of circumstances These conditions are summarized by Scott, Matthews, Butterworth, and Frommeyer[2] as follows 1) activation of plasminogen as a result of the general alarm reaction, 2) activation of plasminogen as the result of release into the circulation of tissue activator substances, 3) entry into the circulation of proteolytic enzymes other than plasmin from sources such as the prostate or pancreas, 4) amniotic fluid embolism

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Read at annual meeting of Western Section of American Urological Association San Francisco Calif April 30–May 3, 1956

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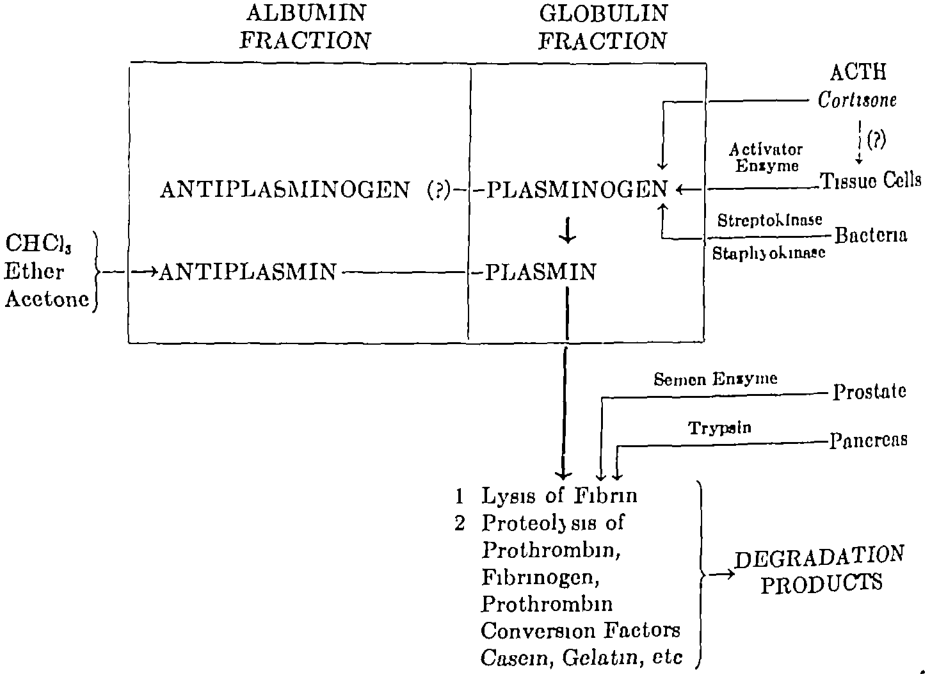

Fig 1 Schema of plasma proteolytic enzymes and proposed mechanism of action of various compounds, bacteria and tissue products

MacFarlane and Biggs[4] and Biggs, MacFarlane and Pilling[5] have shown that such stimuli as fear, exercise, trauma and parenteral adrenalin may initiate an increased plasmin activity These investigators have demonstrated plasminemia in approximately one half of the preoperative patients they studied In addition, their studies show that plasminemia occurs in approximately one half of post operative patients without relation to the severity of the surgery Tagnon and associates recorded *fibrinolytic activity in cases of severe burns,* hemorrhages and barbiturate poisoning In view of these and other studies the alarm reaction of Selye is postulated as the basic mechanism for abnormal plasma proteolytic activity

Many studies support the postulation that plasminogen is activated as a result of release into the circulation of tissue activator substance Lung tissue has been shown to be particularly capable of causing activation of plasminogen in the studies of Tagnon and Petermann[6] and Mathey et al[7] Tagnon and Petermann also demonstrated an activator of plasminogen in many other organs Astrup and

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Permin[8] suggest that all tissue cells are capable of activation of plasminogen Neoplastic tissue may also be capable of activation of plasminogen since Coon and Hodgson[9] reported a patient with bronchogenic carcinoma who had plasminemia After surgical removal of the tumor the plasminemia disappeared

Abnormal proteolytic activity is postulated to occur following entry into the circulation of proteolytic enzyme from the pancreas or prostate Proteolytic activity has been observed during or following pancreatic surgery The clinical picture of proteolytic activity due to trypsin is not dissimilar to that due to plasmin The work of Kaplan[10] makes clear the differentiation of trypsin and plasmin An enzyme originating in the prostate gland has been shown by the studies of Huggins and Neal[11] and VonKaulla and Shettles[12] to have the same proteolytic properties of plasmin This semen enzyme system was found to have a precursor or proenzyme and an antienzyme Tagnon et al [13] [14] have demonstrated that prostatic cancer tissue and metastatic prostatic carcinoma cells contain a proteolytic enzyme that is able to digest fibrinogen and fibrin Tagnon points out the analogy of increased plasma proteolytic activity in extensive metastatic prostatic carcinoma to other such cases with an elevated serum acid phosphatase Since a transient elevation of the serum acid phosphatase is noted following massage of the prostate gland it is not unreasonable to conjecture that the more severe trauma of a prostatic operation could result in the intravascular release of all other enzymes or enzyme activators produced by prostatic tissue If sufficient enzyme or enzyme activators gain access to the bloodstream to neutralize the powerful inhibitors of proteolytic enzymes in the blood serum[15] fibrinolysis may occur The actual cause of fibrinolysis associated with prostatic surgery is unknown The process may be entirely due to the intravascular release of the semen proteolytic system or due to intravascular release of enzyme activators from the prostate triggering the plasmin system The pathogenesis in prostatic surgery may conceivably be the general alarm reaction with subsequent activation of plasminogen

METHODS

Coagulation time of venous blood The modified Lee-White method was used for determination of the coagulation time

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Plasma fibrinogen concentration The modified Ware and Seegers[16] method was used for determination of the plasma fibrinogen concentration

Histopathology of prostatic tissue In addition to the routine histopathology available at our hospital, the tissues in these cases, where practical, were studied by the blended tissue method of Ludden and Jensen [17] This was undertaken to leave little doubt that fibrinolysis had occurred in benign prostatic hypertrophy

The following 5 case reports illustrate hypofibrinogenemia and afibrinogenemia in transurethral prostatic resections One case occurred in adenocarcinoma of the prostate and 4 cases in benign prostatic hypertrophy

CASE REPORTS

Case 1 G T, a 70-year-old white man, was admitted to the hospital because of urinary obstruction due to benign prostatic hypertrophy Under spinal anesthesia a transurethral resection of the prostate gland was performed Thirty grams of tissue were removed in one hour Whole blood was started near the end of the procedure because of uncontrolled oozing from the prostatic fossa No open venous sinuses were identified Immediately after operation the clotting time was 60 minutes and the clot completely lysed in 3 hours The patient continued to bleed through the urethral catheter and all modes of catheter traction upon the prostatic fossa failed to abate the bleeding Blood loss was replaced with whole blood The sites of venipuncture, venesection and the site of lumbar puncture for the spinal anesthetic oozed profusely A few hours postoperatively urethroscopy was performed to possibly identify bleeding points Again generalized oozing from the prostatic fossa was noted and not controlled by fulguration Toluidine blue and fibrinogen were not available for administration at this time A fibrinogen determination 20 hours postoperatively was 106 mg per cent During the postoperative course the patient received 5,400 milliliters of whole blood The blood pressure progressively declined and 22 hours postoperatively the patient expired

Case 2 R H, a 75-year-old white man, was admitted to the hospital because of acute urinary retention due to benign prostatic hypertrophy Under spinal anesthesia a transurethral resection of the prostate gland was performed Toward the end of the resection the patient had an acute asthmatic attack controlled by intravenous ephedrine and aminophyllin Twenty four grams of prostatic tissue were resected Venous sinuses were opened near the end of the procedure, but bleeding was easily controlled by catheter traction The blood pressure and pulse were stable throughout surgery Subsequently the blood pressure progressively declined and profuse bleeding developed through the urethral catheter This bleeding was not controlled by traction, therefore, urethroscopy was performed Fulguration would not control the generalized oozing from the prostatic fossa A blood sample was found to have no fibrinogen and no heparin A blood sample at this time did not clot in one hour The patient expired 4½ hours postoperatively before any fibrinogen was instituted

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[17] Ludden, T E and Jensen, R E Histologic diagnosis of cancer by study of blended tissues with particular reference to adenocarcinoma of prostate J Urol, 72 57, 1954

Case 3 J F an 81-year-old white man, was admitted to the hospital because of acute urinary retention due to a small fibrotic benign prostate Under spinal anesthesia a transurethral resection of the prostate gland and bladder neck was performed The obstruction was relieved with resection of only 7 gm tissue Good hemostasis was acquired at surgery, but during the operation the patient had acute precordial pain An electrocardiogram at this time showed no changes from one taken preoperatively The blood pressure remained stable until 2 hours postoperatively at which time there was an increase in blood pressure to 150/70 from a baseline of 110 70 Three hours postoperatively profuse bleeding through the urethral catheter developed and the patient vomited coffee ground emesis positive for blood Bleeding from the oral mucous membranes was also noted at this time A blood sample 4 hours postoperatively contained no fibrinogen In further support for the diagnosis of plasminemia it was found that the patient's plasma lysed a normal homologous blood clot and also lysed his own blood clot Therapy therafter consisted of whole blood transfusions, toluidine blue and 6 gm fibrinogen (1 gm hourly for the subsequent 6 hours) At 18 hours postoperatively the plasma fibrinogen concentration was 100 mg per cent The patient expired 19 hours postoperatively

Case 4 P G, a 70-year-old white man was admitted to the hospital because of acute urinary retention and hematuria 2 days before admission The hematuria completely subsided on indwelling catheter drainage and a complete urological workup revealed no genitourinary disease other than benign prostatic hypertrophy Under spinal anesthesia a transurethral resection of the prostate gland was done In 70 minutes 47 gm were resected Near the end of the procedure the capsule was perforated A cystogram revealed extraperitoneal extravasation The blood pressure had remained stable throughout surgery with the administration of 600 ml whole blood The patient s general condition was satisfactory and there was no unusual bleeding A cystostomy and drainage of the prevesical space were undertaken immediately As the skin was being closed the patient vomited bright red blood and the sites of recent venipunctures began bleeding Also profuse bleeding developed through the urethral catheter At this time the patient s plasma fibrinogen concentration was 141 mg per cent and his clotting time was 20 minutes In 1 hour the clot was completely lysed Intravenous therapy consisted of toluidine blue 6,800 ml whole blood and 1 gm fibrinogen administered every hour for the subsequent 6 hours Vasopressors were also employed to maintain the blood pressure Subsequently the blood pressure declined and the patient expired 22 hours postoperatively

Case 5 S H an 82-year-old white man, was admitted to the hospital because of elevated residual urine due to adenocarcinoma of the prostate gland proven by Silverman needle biopsy The patient had been previously on estrogen therapy 2 months No metastatic disease was evident by chest film or bony survey films Under spinal anesthesia a transurethral resection of the prostate gland removed 14 gm tissue During the resection venous sinuses were entered, but good hemostasis was acquired and the patient maintained a normal blood pressure This case was operated upon at a time when a study of fibrinogen concen-

TABLE 1 *Effects of hyperheparinemia and plasminemia on blood clotting*

Hyperheparinemia	Plasminemia
1 Coagulation time is usually delayed	1 Coagulation time may be normal or may be infinitely delayed
2 Small amounts of the patient's blood will delay the coagulation time of normal blood	2 The patient's blood will not delay the coagulation time of normal blood
3 Addition of small amounts of thrombin will usually produce a clot	3 If blood does not clot spontaneously thrombin will not cause clotting
4 If a clot forms it does not lyse	4 If a clot forms it will partially or completely lyse within 24 hours

trations was being done In this study fibrinogen determinations were done preoperatively, 1 hour following the administration of the anesthetic and 4 hours after the anesthetic The preoperative fibrinogen concentration was 280 mg per cent and the 1 hour postanesthetic plasma fibrinogen concentration was 336 mg per cent Almost simultaneously with the report from the laboratory of the 4-hour postanesthetic blood sample containing no fibrinogen the patient suffered profuse bleeding through the urethral catheter and a blood pressure drop Treatment immediately instituted consisted of toluidine blue, whole blood transfusions and 1 gm of fibrinogen every hour for the subsequent 5 hours Bleeding through the urethral catheter gradually decreased The plasma fibrinogen concentration 24 hours postoperatively was 340 mg per cent Within this postoperative period 5,600 milliliters of whole blood were given At 48 hours postoperatively the drainage through the urethral catheter was grossly clear of blood At 72 hours the plasma fibrinogen concentration was 340 milliliters per cent The patient has been followed 3 months postoperatively without recurrence of bleeding

DIAGNOSIS

After the well defined hemorrhagic diatheses are excluded, hyperheparinemia and plasminemia should be considered in the differential diagnosis of excessive bleeding during or following operative procedures Table 1 outlines the effects of hyperheparinemia and plasminemia on blood clotting The diagnosis can be made by careful observation of the blood while determining the modified Lee-White coagulation time This test, of course, should be started before any therapy is instituted since therapy may obscure the test It should be emphasized that therapy need not be delayed while this test is being run since considerable time may elapse while the future integrity of the clot is being decided When the blood is obtained for this test a specimen may also be obtained for determination of the plasma fibrinogen concentration During observation of the blood any one of the following phenomena may occur in plasminemia 1) the coagulation time may be normal with ensuing partial lysis of the clot, 2) the coagulation time may be normal with ensuing complete lysis of the clot, or 3) there may be no coagulation Hyperheparinemia will not cause lysis of the blood clot, therefore, if a clot forms, hyperheparinemia is ruled out From this it is evident that the blood in both hyperheparinemia and plasminemia may not clot To differentiate the two in such a condition a small amount of thrombin is added Thrombin will usually produce a clot in hyperheparinemia

TREATMENT

We can not predicate the therapy of fibrinolysis occurring in prostatic surgery with the experience of only 5 cases Cases 3, 4, and 5 were treated similarly with whole blood, fibrinogen and toluidine blue Apparently one of the most important factors is early recognition Once fibrinolysis is suspected and the blood samples are drawn the therapy should be started empirically If the blood sample does not clot and there is difficulty in immediately distinguishing hyperheparinemia and plasminemia, an antiheparin such as toluidine blue should be given The recommended dosage of toluidine blue is 5 mg per kilogram of body weight If a blood sample 30 minutes after injection of toluidine blue does not clot or demonstrates a prolonged coagulation time, this is strong evidence that one is not dealing with hyperheparinemia

When either a normal coagulation time or a delayed coagulation time is demonstrated, therapy must also be instituted for plasminemia Our therapy has consisted of the intravenous administration of whole blood and fibrinogen

Whole blood acts upon the abnormal plasma proteolytic activity both directly and indirectly The *direct* action is in the supplementation of the patient's plasma with antiplasmin content of normal plasma found in the albumin fraction A disadvantage of whole blood is its normal content of plasminogen or plasmin found in the globulin fraction With more plasminogen available to the patient's enzyme activating system the abnormal proteolytic activity could be augmented The *indirect* action of whole blood on plasminemia or fibrinolysis is in the supplementation of substrate in the form of fibrinogen, prothrombin and other coagulation factors

We have used 1 gm fibrinogen every hour until clinical evidence of lessening of bleeding Fibrinogen is given to supply large amounts of substrate

We have had no experience in the treatment of plasminemia with low salt human serum albumin, but this appears to be an advisable mode of direct attack It is in the albumin fraction of blood that antiplasmin resides With the administration of albumin it is possible to supply the patient directly with concentrated antiplasmin which opposes the proteolytic action of excessive plasmin The recommended dosage of low salt human serum albumin is 100 ml every hour until there is clinical evidence of lessening of bleeding One may ask why serum albumin is used in fibrinolysis thought to be caused by prostatic proteolytic enzyme since it is not known whether the albumin fraction of the serum contains an antienzyme for the prostatic proteolytic enzyme Until there is further evidence and conclusions are drawn as to the identity of the prostatic proteolytic enzyme and plasmin it would seem advisable to administer serum albumin to any patient with abnormal proteolytic bleeding

Stefanini and Gendel[18] and Solomon and Stefanini[19] have reported striking and prompt falls in plasma proteolytic activity with the use of cortisone or corticotrophin in patients with excessive fibrinolysis We have not evaluated this therapy in our cases

In summary the important factors in treatment should include early recognition of abnormal bleeding, early empirical therapy, whole blood in amounts to maintain blood volume and blood pressure, neutralization of the proteolytic enzyme with serum albumin and fibrinogen, and employ cortisone or corticotrophin to increase the circulating antienzyme

SUMMARY

A clinical and laboratory summary of the findings in 5 cases of fibrinolysis following surgical removal of the prostate is presented Simple laboratory procedures are suggested to alert the surgeon of this impending complication and the present methods of treatment are briefly discussed

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[18] Stefanini, M and Gendel, B R Influence of fibrinolysin on the survival in vivo of various coagulation factors and favorable effect of cortisone on "fibrinolytic purpura " Clin Res Proc , 1 5, 1953

[19] Solomon, L and Stefanini, M Control of bleeding manifestations in "fibrinolytic states" by corticotropin and cortisone Clin Res Proc , 2 33, 1954

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RETROPUBIC PROSTATECTOMY

HARRY G COOPER

This paper is a review of 500 retropubic prostatectomies that I performed during the years 1947–1955 A comparison is made with other types of prostatectomies carried out by other surgeons, as well as myself

The popularity of the retropubic approach has increased (table 1) In the 3-year period, 1950–52, twice as many retropubic prostatectomies were done as in the previous 3-year period, the incidence has remained fairly constant since that time at approximately 25 per cent of all prostatectomies This is contrary to the opinion of some authors who have reported that the retropubic is the proper or best approach in the *majority* of cases We considered it the best approach in 25–30 per cent of cases

SIZE OF GLAND

The size of the gland that can be removed successfully by the transurethral approach depends entirely upon the dexterity of the urologist, it has become more or less apparent that large glands are removed adequately by the transurethral approach only by repeated operations

In 1947 we decided that 60 gm was the maximum amount of tissue which we should remove transurethrally It is difficult to estimate gland weight in situ and, despite the routine use of the excretory urogram, cystogram, endoscopy, and palpations, we frequently find our preoperative estimate at considerable variance with the weight which is recorded by the pathologist

For a period of 8 months in 1949 I used the retropubic approach exclusively in an effort to determine the optimal size of gland for removal by this method It became apparent that small, fibrotic glands weighing less than 20 gm were difficult to remove retropubically, and that the postoperative course was more stormy, and the complications more numerous than when larger glands were removed

ADVANTAGES OF THE RETROPUBIC APPROACH

1) It would appear to be sound surgery to use an extravesical approach to an extravesical organ, there is minimal trauma to the penile urethra, seminal vesicles, and urinary bladder

2) The large adenoma is removed under direct vision and the prostatic bed can be completely evacuated, leaving no tag ends as nidi for infection or subsequent proliferation

3) It is much less shocking to the patient than opening the bladder

4) No persistent urinary sinus should follow retropubic prostatectomy if it is well done There have been none in the 500 cases in my series

5) The incidence of urethral stricture is markedly reduced

Read at annual meeting of Western Section of American Urological Association, San Francisco, Calif April 30–May 3, 1956

TABLE 1 *Types of prostatectomy Comparison of number of prostatectomies performed through different approaches during three 3 year periods*

	1947–48–49	1950–51–52	1953–54–55
Transurethral prostatic resection	468	542	572
Suprapubic	119	66	36
Perineal	48	29	8
Retropubic	98	199	204
	—	—	—
	733	836	820

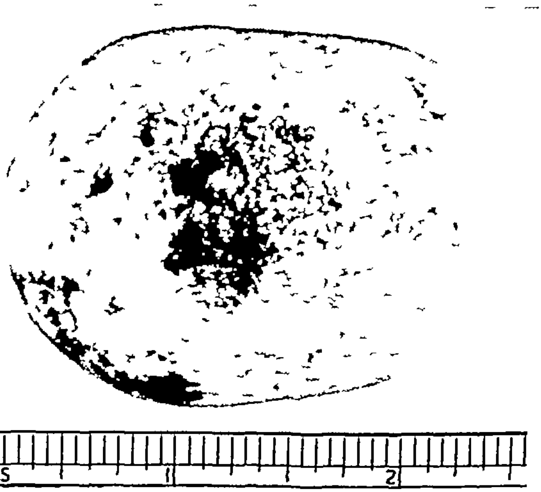

FIG 1

6) The technique is easier to teach than is the transurethral, it is, however, extremely difficult to master without a teacher

7) The mortality is very low

8) Complications are no more frequent than following other types of prostatectomy

9) Bladder stones of almost any size can be removed at the same operation (fig 1)

DISADVANTAGES OF THE RETROPUBIC APPROACH

The technique is more difficult than the suprapubic

It is not suitable for removal of small fibrotic glands

Tumors and diverticula of the bladder cannot be as easily treated as when either a transurethral or suprapubic approach is used

Incisional hernia is a potential complication (three in our series)

Experience has taught me that a thick anterior abdominal wall is *not* a contraindication to the retropubic approach The space of Retzius can now be entered with impunity The retropubic operation, as designed by Millin, and the controlled use of antibiotics have nullified the reputed dangers, and the space of Retzius is no longer "forbidden territory"

TABLE 2 *Age of patients at time of operation*

	Years	Average Age
		yr
Transurethral prostatic resection	30–95	60
Suprapubic	57–88	74
Perineal	42–77	70
Retropubic	45–89	73

TABLE 3 *Weight of tissue removed through the different approaches*

	Weight	Average Weight
	gm	*gm*
Transurethral prostatic resection	1–120	16.4
Suprapubic	12–196	64.0
Perineal	16–106	23.0
Retropubic	8–365	52.5

TABLE 4 *Blood loss at operation*

	gm.	cc
Transurethral prostatic resection	14	260
Suprapubic		
No hemostasis	50	368
Gauze pack	62	510
Oxidized gauze with Foley catheter	50	210
Pilcher bag	50	640
Perineal		
Simple		458
Radical		918
Retropubic		640

AGE OF PATIENT

As shown in table 2, age is not an important criterion as to which type of operation should be performed. The average age for the transurethral is significantly lower than the others, and the range in age greater.

WEIGHT OF TISSUE REMOVED

The amount of tissue removed through the different approaches is given in table 3. It would probably have been better to have removed the 120 gm. prostate through the suprapubic approach and the 8 gm. gland by the transurethral approach.

BLOOD LOSS AT OPERATION

Table 4 is a summary of work done by Goodyear and Beard of Atlanta, Georgia, who measured fairly accurately the blood loss of patients during 100 prostatectomies.

Our method of measuring blood loss was not so detailed, but our experience indicated that the loss was not quite so much by the perineal route, i.e., 918 cc,

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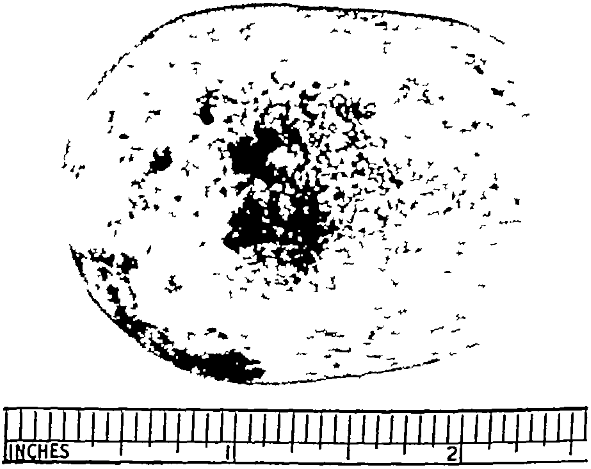

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7 1 as section

	Cases	Per Cent Epididymitis
Transurethral	3	9 4
Suprapubic	2	10 0
Perineal	1	11 0
Retropubic		
T	1	10 0
	1	
Transurethral	1	10 4
Suprapubic	1	
Perineal		
Retropubic		

ture

	Strictures	Per Cent
Transurethral pro	129	8 15
Suprapubic	10	4 71
No hemostasis	3	3 15
Gauze pack	20	4 00
Oxidized gauze		
Pilcher bag		
Perineal		
Simple		
Radical		
Retropubic		

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as Goodyear and Beard report For the first 2 years of our experience with the retropubic, our blood loss was comparable to, or even in excess of theirs (640 cc) With increased skill and improved technique our average blood loss is between 150–500 cc, a figure of relative insignificance

COMPLICATIONS

Secondary hemorrhages Postoperative hemorrhage has occurred up to 35 days The incidence (table 5) is much higher than those reported by others, but it is our policy to take all cases back to surgery if the blood is not easily evacuated on the ward This procedure is not practiced uniformly in other institutions and the hemorrhages which occur on the wards are not usually included in the statistics I attribute our relatively low mortality in some measure to this practice of immediate evacuation in all types of prostatectomy In 95 per cent of cases the bleeding point could not be identified after evacuation of the blood

Epididymitis This annoying complication (table 6) shows the same incidence as table 5 It may be considered high but these figures include all those patients in whom epididymitis developed within 6 months after operation

Vas ligation In 1953, one hundred cases were observed in an attempt to answer the controversy in regard to the incidence of epididymitis with or without vas section or ligation Three different surgeons were involved, some patients were treated with vas section, some with ligation, and some with no preventative treatment This applied only to three types of prostatectomies The results showed that the incidence of epididymitis did not vary appreciably whatever preventative measures were taken (table 7)

As a result of this study vas section or ligation has been discarded as a routine procedure and, with the recent increased incidence of staphylococcal infections, we believe the procedure is contraindicated

Stricture Recognized authorities estimate the incidence of strictures following transurethral prostatic resection as anywhere from 1 5 per cent (Taylor) to 25 per cent (O'Brien) In this series the incidence of stricture following transurethral is at least twice the rate of any of the other procedures (table 8) the overall incidence being 6 75 per cent It has been our experience that stricture of the

TABLE 5 *Secondary hemorrhages*

	Per Cent
Transurethral prostatic resection	9 00
Suprapubic	12 00
Perineal	1 30
Retropubic	12 00

TABLE 6 *Epididymitis*

	Per Cent
Transurethral prostatic resection	12 00
Suprapubic	8 00
Perineal	0 00
Retropubic	10 52

TABLE 7 *Vas section*

	Cases	Per Cent Epididymitis
Transurethral prostatic resection		
32 ligated	3	9.4
20 nil	2	10.0
9 section	1	11.0
Suprapubic		
4 ligated		
4 nil	1	10.0
2 section		
Retropubic		
10 ligated	1	
10 nil	1	10.4
9 section	1	

TABLE 8 *Stricture*

	Cases	Strictures	Per Cent
Transurethral prostatic resection	1,582	129	8.15
Suprapubic	221	10	4.71
Perineal	95	3	3.15
Retropubic	501	20	4.00

vesical neck is slow in developing with some of the retropubics, so that, as time goes on, the incidence of this complication may increase

Fistulas Chronic suprapubic fistula is almost a thing of the past, due to antibiotics and improved nursing care, however, they still occur Millin reported in one series an incidence of fistula of 4.2 per cent following retropubic prostatectomies Others have reported an incidence as high as 12 per cent The incidence in this series so far is 0 per cent The fact that we have never had a cutaneous fistula following retropubic prostatectomy we believe to be due, in part, to the practice of using as little catgut as possible, and no hemostatic sutures or cautery in the capsule, thus avoiding foreign body granulomatous reaction The use of the sump drain (fig 2) may also have been a contributing factor

It was first advocated by Aberhart of Toronto It is a red rubber tube inside a large, perforated, plastic tube It is placed at the bottom of the space of Retzius, lying on the resutured prostatic capsule Continuous suction is used for 48 hours to minimize pooling of blood serum and extravasated urine, then the whole drain removed

Incontinence See table 9

This distressing complication follows *all types of prostatectomies* Fortunately, it is not common In a number of instances incontinence developed to a greater or lesser degree and the figures include those cases of minimal stress incontinence where patients lose a few drops of urine when under stress, or when coughing, or changing position, etc , as well as those who have complete loss of control and must employ some mechanism to make life comfortable The majority as Goodyear and Beard report For the first 2 years of our experience with the retropubic, our blood loss was comparable to, or even in excess of theirs (640 cc) With increased skill and improved technique our average blood loss is between 150–500 cc, a figure of relative insignificance

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TABLE 6 *Epididymitis*

	Per Cent
Transurethral prostatic resection	12 00
Suprapubic	8 00
Perineal	0 00
Retropubic	10 52

TABLE 11 *Morbidity*

	Average Hospital Days	Months to Return to Normal
ransurethral prostatic resection	14.0	1–6
uprapubic	22.0	1–4
erineal	30.0	1–6
etropubic	16.4	1–3

TABLE 12 *Osteitis pubis*

	Cases	Osteitis	Per Cent
Others	116	13	11.50
Millin	757	35	4.60
This series	501	2	0.40

TABLE 13 *Mortality, 2,399 prostatectomies*

	Per Cent
38 deaths—mortality rate	1.59
Transurethral prostatic resection	1.43
Suprapubic	3.30
Perineal	3.70
Retropubic	1.62

TABLE 14 *Causes of death*

38 cases, 37 autopsies

Heart	17
Lung—including emboli (8)	18
Renal	10
Miscellaneous	10
	55
Multiple causes	17
Total	38

course, whereas the retropubic patient *often* has a stormy course postoperatively. However, when the retropubic patient leaves the hospital he is usually free from all discomfort and within a month is completely cured, whereas the patient who has undergone transurethral prostatic resection often complains of frequency, burning, nocturia, dysuria, hematuria, for a period of up to 6 months after operation. We encounter these patients in outpatient followups; investigation almost invariably reveals pyuria or stricture or high urinary residue in most of those still complaining after 1–3 months. Thus, immediate morbidity in the retropubic group is higher but is of a much shorter duration. These statistics (table 11) were obtained almost entirely from D.V.A.* Hospital and figures are much higher than those in private practice, but this is because we do keep our out-of-town patients under surveillance for a longer period of time for obvious reasons.

* Department of Veterans Affairs

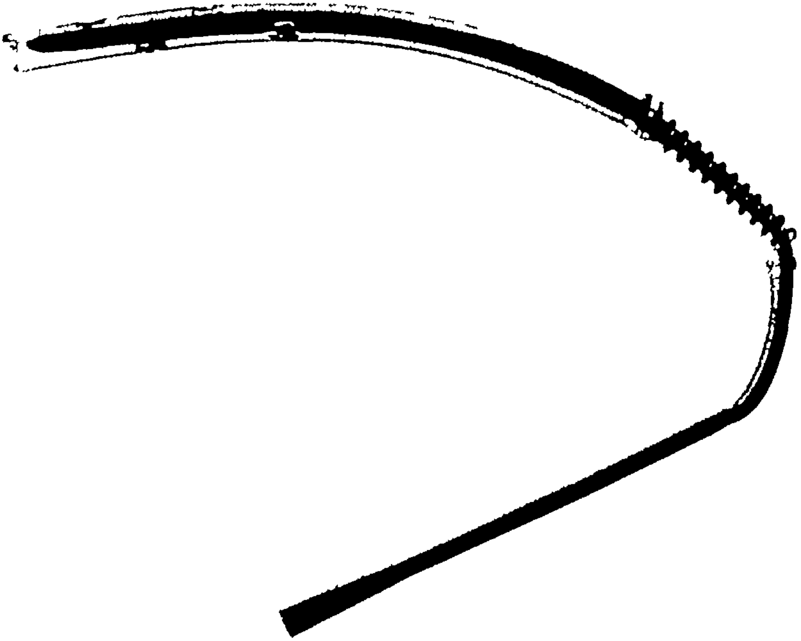

Fig 2

Table 9 *Incontinence*

	Cases	Per Cent
Transurethral prostatic resection	9	0 56
Suprapubic	2	0 65
Perineal	4	1 21
Retropubic	3	0 60

Table 10 *Re operation*

	Cases	Per Cent
Transurethral prostatic resection	63	1 00
Suprapubic	1	1 25
Perineal	1	1 00
Retropubic	7	1 12

of those with complete lack of control are in the senile group where it is impossible to re-educate the perineal muscles to control the external sphincter

Re-operation See table 10 In addition to those patients who undergo transurethral prostatectomies other types require an additional operation Among the transurethral cases there is usually some residual prostatic tissue, whereas in the others it is due to contracture of the vesical neck All re-operations are by the transurethral route

The transurethral prostatic resection has, by quite a large margin, the shortest stay in hospital and usually the patient does not have a stormy postoperative

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NONSPECIFIC CORTISONE EFFECTS FROM ACTH ADMINISTRATION IN ADVANCED PROSTATIC CARCINOMA

FRANK HINMAN, JR AND GILBERT I SMITH

From the Subdivision of Urology, University of California School of Medicine, San Francisco, Calif

Cortisone therapy for advanced prostatic carcinoma produces a significant proportion of clinical remissions[1, 2, 3] Whether this action is due to adrenal suppression with the resulting decrease in androgenic activity ("medical adrenalectomy"), or to the direct effect of cortisone on the patient and the neoplasm has not been known

Adrenocorticotropin gel can stimulate the adrenals to produce a level of circulating corticoids equal in biologic activity to that from administered cortisone This could be a means of differentiating adrenal suppression from cortisone effect (fig 1) If ACTH produced *no* remission in patients with advanced prostatic carcinoma it could then be assumed that cortisone probably acts through adrenal suppression (the anti-androgenic effect that has been assumed heretofore) On the other hand if remissions *were* observed, it would be more likely that cortisone therapy exerts its effect by direct cortisone action (nonspecific hormonal effect)

POSSIBLE MODES OF ACTION OF CORTISONE

Cortisone causes clinical improvement in advanced prostatic carcinoma, and even shrinkage of the local prostatic lesion without significant change in the level of serum acid phosphatase or in the demonstrable metastases[2, 3] Several mechanisms could explain these effects

1 *Adrenal suppression* Cortisone is known to inhibit ACTH production and so cause adrenal atrophy[4] Since some of the steroids from the adrenal are androgenic castration plus cortisone administration will cause the 17-ketosteroids to fall to a low level, approaching that reached after adrenalectomy[5] This effect of cortisone therapy has been assumed to produce the clinical response in advanced prostatic carcinoma (i e "medical adrenalectomy")

2a *Direct pharmacologic effect* Cortisone has been called the magnificent aspirin and has indeed many of the effects of this drug[6] That cortisone can produce a sense of well-being is an accepted fact

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Read at annual meeting of Western Section of American Urological Association San Francisco Calif April 30-May 3, 1956

Supported by American Cancer Society Institutional Grant

[1] Hayward, W G Treatment of late relapse of prostatic carcinoma by cortisone J Urol 69 152 1953

Valk W and Owens R H Effect of cortisone on patients with carcinoma of the prostate J Urol, 71 219 1954

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[5] Leadbetter W F Ganem E J and Solomon, D H Experiences with bilateral adrenalectomy and use of cortisone in treatment of advanced carcinoma of the prostate Tr Am Assn G U Surg 44 65-80, 1952

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OSTEITIS PUBIS

Osteitis pubis is an entity of which little is known In our cases the incidence fortunately has been quite low and occurred in case Nos 268 and 280 Osteitis pubis developed in the latter case 4 weeks following retropubic prostatectomy The patient was returned to the operating room and the space of Retzius re opened in an effort to determine the etiological factor However, there was no evidence of pathological change Biopsy of areolar tissue, scar tissue, as well as periosteum of symphysis pubis was taken for smear and culture, all reports were negative

It is apparent that the mortality of the retropubic prostatectomy is low and compares favorably with the transurethral Causes of death are listed in table 14 Thirty-seven autopsies were obtained of the thirty-eight deaths Multiple causes of death were present in 17 cases Those related to the heart include coronary occlusion, toxic myocarditis, myocardial degeneration, arteriosclerotic heart dis ease, hypertensive heart disease, acute pericarditis

Those of the lung include pneumonia, pulmonary edema, pulmonary embolus

Those of the kidney include pyelonephritis, lower nephron nephrosis (2 cases)

Miscellaneous diagnoses include perforation of bladder, gangrene of bladder, cerebral hemorrhage of infarction, septicemia due to phlebitis, idiopathic intestinal hemorrhage, acute yellow atrophy, postoperative shock, amebiasis

SUMMARY AND CONCLUSIONS

A review of 501 retropubic prostatectomies has been made and comparisons have been drawn with the older types of operations, as well as comparison with retropubic method reported by others

There is no doubt that the retropubic approach has a place in treating the obstructing prostate It is not the complete answer to the treatment of this serious problem, but it has many advantages and few disadvantages Technically, it is a more difficult operation than the suprapubic, but the mortality rate is lower and no fistulas should occur Strictures are less common following retropubic prostatectomies than following transurethral prostatectomies Incontinence and impotence are less common following retropubic prostatectomies than following perineal prostatectomies

All four types of prostatectomies have their place No single procedure answers all problems, and I quote Doctor Rush with whom all urologists should be in agreement "The method of prostatectomy should be adopted to meet the needs of the patient, not the patient forced to conform to the limited skill of the surgeon "

The urologist cannot neglect any avenues of approach to the prostate, but should master them all

I wish to acknowledge that information listed in the different tabulations has been derived, in part, from the records of Shaughnessy Hospital, Department of Veterans Affairs, Vancouver, Canada

925 W Georgia St , Vancouver, B C , Canada

The rise in urinary excretion of 17-ketosteroids would be expected therefore to be accompanied by an increase in androgenic effect during administration of ACTH to patients with prostatic carcinoma Such androgenic effect would usually increase the rate of growth of prostatic carcinoma (although not invariably so[5])

ACTH, however, simultaneously stimulates production of cortisone-like substances, which can be measured by the excretion of 17-hydroxycorticoids[13] It is this "cortisone" which might be expected to act like orally-administered cortisone acetate So ACTH might produce similar clinical remissions were the effect due to cortisone and not to an anti-androgenic mechanism

EFFECTS OF ACTH THERAPY ON OTHER NEOPLASMS

ACTH has been administered to patients with "hormonal" lesions and to those with neoplasms not under hormonal influence Taylor and Morris[14] obtained a 10-day remission in one woman with carcinoma of the breast, but a second patient was made worse Two patients with other nonhormonal neoplasms (carcinoma of the trachea and Ewing's tumor) were clinically improved, although no evidence of actual regression of the lesions was seen Further, these workers[15] [16] treated 26 other patients and obtained beneficial nonspecific effects without regression of the tumor They suggest that these results may represent inhibition of the local tissue reaction to the tumor Four patients with carcinoma of the breast were included, one was made worse but 2 were clinically improved, one showing actual regression of skin nodules

Eliel and Pearson,[17] in contrast, found no measurable effect of ACTH or cortisone on patients with carcinoma of the prostate, breast, or adrenal, nor on a number with "nonhormonal" neoplasms

Other similar studies with ACTH have been reported, some showing temporary improvement[18-22] The latest, by McCarthy,[23] describes the combination

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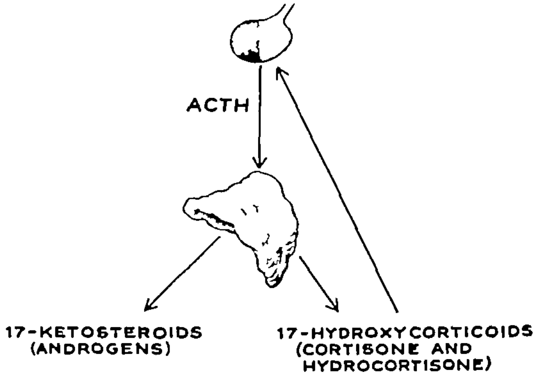

FIG 1 Schema of relationships between ACTH stimulation and corticoid suppression

b "Nonhormonal" anti-inflammatory effect Cortisone has been reported to have a nonspecific effect on a variety of tumors known to be free of hormonal influences, acting on lymphocytes, or on collagen or other elements of the connective tissue The spreading factor via the hyaluronidase system may be affected

c Protein catabolic effect Protein synthesis might be impaired (as shown by Parson and Crispell[7] in radioglycine studies) or cell catabolism promoted Effects on carbohydrate metabolism are only speculative at present

d Hormonal shift Cortisone may act by altering the hormonal-metabolic environment Any such change may make a tumor which has acquired resistance to a certain hormonal balance more vulnerable to the new environment An example is the temporary suppression of estrogen-resistant prostatic carcinoma by testosterone [8]

HORMONAL EFFECTS OF ACTH ADMINISTRATION

ACTH causes increased excretion by the adrenal cortex of 17-ketosteroids, principally dehydroisoandrosterone, which is a normally occurring urinary androgen[9, 10] of appreciable biologic activity On the other hand, although hydrocortisone or cortisone given after adrenalectomy will produce a rise in 17-ketosteroid excretion equal to that occurring after simple castration, the androgenic activity of the urine in such cases is much lower [11] These facts strongly suggest that the normal adrenal produces biologically effective androgens which have precursors other than cortisone or hydrocortisone In fact, recent work shows that biologically effective androgens more than double after ACTH administration [12] third had no benefit from cortisone nor subsequently received any from ACTH These few responses support the concept that ACTH and cortisone act in parallel fashion, and that corticoids rather than adrenal suppression are directly responsible for the clinical effect

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The urinary excretions of 17-hydroxycorticoids and 17-ketosteroids were found to roughly parallel each other Corticoid excretion indicated the relative effectiveness of the administered ACTH (table 2) Three patients showed a good rise in corticoid excretion (to 38 5, 42, and 88 mg per 24 hours respectively), 2 of these had significant clinical improvement Two patients had a slight rise (to 10 4 and 13 mg /24 hours respectively), one had significant clinical improvement and the other had slight temporary improvement Two patients had no change in corticoid excretion, neither of these patients had clinical improvement In addition, one patient who had a 9-week remission had no post-treatment determinations (table 3)

The local lesion, acid and alkaline phosphatase and bony metastases manifested no change unless it was toward progression of the neoplasm (table 4) In one patient there was a questionable softening of the local lesion In our previous cortisone series, 6 of 10 patients had improvement in the local lesion

The clinical value of ACTH therapy in this brief series is seen to be slight

TABLE 1 *Relation between response to orchiectomy and stilbestrol, cortisone, and ACTH therapy*

Case No	Age	Previous Response to Orchiectomy and Stilbestrol	Previous Response to Cortisone	Response to ACTH	Subsequent Response to Cortisone
				weeks	
1	69	+	No response	0	No effect
2	74	++		3	Pain decreased
3	70	0		1½	
4	52	+		8	3 mo remission
5	63	++	Relieved pain 1 mo	0	No effect
6	77	0	15 mo remission	0	
7	75	++		>10	
8	65	+		9	

* 0 = less than 6 months
+ = 6–12 months
++ = greater than 12 months

TABLE 2 *Relation of clinical response to adrenal stimulation*

Patient No	17-Hydroxycorticoid Rise	17-Ketosteroid Rise	Clinical Effect
2	5 7–42	3 6–21 8	Improved 3 wks
3	4 0–13	2 8– 3 9	Improved 1½ wks
4	10 8–88	7 0–44	Improved 8 wks
6	7 7–38 5	8 6–11 5	No improvement
7	3 6–10 4	2 3– 5 1	Improved more than 10 wks

of ACTH or cortisone with nitrogen mustard ACTH was less effective than cortisone in this combination in cases of breast and prostatic carcinoma

The present experiment consisted of the administration of ACTH to patients in exacerbation with advanced prostatic carcinoma, to compare its action with that of cortisone, which we had previously studied

CLINICAL EXPERIMENT

Eight patients were studied

1 *Selection of patients* was limited to those who were in relapse after orchiectomy plus stilbestrol administration (and in some instances after cortisone therapy) These patients provided their own controls, since a steady downhill course was inevitable and spontaneous remissions extremely unlikely All had assessable symptoms, particularly pain and deterioration, as well as palpable prostatic lesions and metastases visible by x-ray Previous remissions varied from zero to 30 months in duration

The time interval between castration and ACTH therapy was sufficient in every case to allow any compensatory adrenal androgenic hypertrophy to take place (making the adrenal cortex more responsive to stimulation)

2 *Dosage of ACTH* was 80 u per day This amount of ACTH* causes adrenal secretion of urinary 17-hydroxycorticoid titers comparable to that occurring after the administration of 100 mg cortisone acetate daily, which was the standard dose of cortisone used in the previous series[3] KCl† was given in doses of 6 gm daily, to prevent the potassium deficit occurring during adrenal cortical therapy[24] This dosage is the same as that used in the previous experiments using 100 mg of cortisone daily

3 *Compound F and 17-ketosteroid excretion* in the urine was measured and correlated with the clinical effect The excretion of compound F, as 17 hydroxycorticoids, provided the principal measure of the adrenocorticotropic effect of ACTH and acted as a check on the adequacy of dosage and method of administration

4 *Effects on the local lesion, on acid and alkaline phosphatase, and on bony metastases* were assessed by palpation, laboratory determinations and x ray respectively

RESULTS

Cortisone therapy previously had been given to 3 patients (table 1), long enough before ACTH therapy so that adrenal suppression was no longer a factor One who had a 15-month remission with cortisone obtained no relief in relapse when given ACTH experimentally A second patient obtained one month's benefit from cortisone, but likewise was not helped by subsequent ACTH therapy The third had no benefit from cortisone nor subsequently received any from ACTH These few responses support the concept that ACTH and cortisone act in parallel fashion, and that corticoids rather than adrenal suppression are directly responsible for the clinical effect

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* Purified corticotropic gel, generously supplied by Dr David Klein, The Wilson Laboratories

† Potassium chloride enteric coated tablets, "PCS 15", provided freely by Mr Ralph P Fletcher, Stayner Corporation

[24] Liddle, G W Bennett, L L and Forsham, P H Prevention of ACTH induced sodium retention by the use of potassium salts a quantitative study J Clin Invest, 32 1197, 1953

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5	63	——	Relieved pain 1 mo	0	No effect
6	[illegible]	0	15 mo remission	0	
7	75	——		>10	
8	65	—		0	

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We are inclined to believe that the effectiveness of cortisone, and, to a less degree, of ACTH therapy, is exerted through a shift in the hormonal environment of the tumor The fact that prostatic carcinoma becomes resistant to the usual anti-androgenic measures (estrogen administration and castration) indicates that it has adapted itself to altered hormonal requirements Thus it would be expected to be more vulnerable to a new hormonal milieu This hormonal shift by ACTH would be anticipated to be less great than that of cortisone (because of the concomitant secretion of androgens in contrast to their suppression by cortisone) Cortisone therapy in turn would be less effective than adrenalectomy Our clinical observations have shown a similar gradation

SUMMARY AND CONCLUSION

The explanation that remissions of prostatic carcinoma after cortisone therapy were due to suppression of adrenal androgenic function by cortisone ("medical adrenalectomy") was tested by clinical experimentation

ACTH was given to 8 patients in relapse with advanced prostatic carcinoma Five patients had clinically apparent remissions

The data suggest that cortisone exerts its clinical effect on advanced prostatic carcinoma other than by adrenal suppression

TABLE 3 *Relation of adrenal response to clinical effect*

	Remission	Slight Remission	No Remission
Effective rise in corticoid excretion	2		1
Slight rise	1	1	
No rise			2
No determinations	1		

TABLE 4 *Effects of ACTH on objective findings*

Patient No	Local Lesion	Acid Phosphatase (KA units)	Alkaline Phosphatase	Bony Metastases
1	Same			Same
2	Same	15 2, unchanged	1 2, unchanged	Same
3	Same	0, unchanged	1 4, unchanged	Same
4	Not hard,? improved	2, unchanged	20, unchanged	Progressive
5	Same	2, increased	7, decreased	Same
6	Same	1, unchanged	5, increased	Same
7	Same	1 9, increased (20, 26)	4 2, increased	Same
8	Same	3, unchanged	13, decreased	Same

(table 1) It was of considerably less practical value than cortisone therapy Three patients had significant remissions of 8, 9, and 10 weeks respectively, eating better, gaining weight, and being relatively free of pain Two had short periods of improvement, and 3 had no improvement One of those listed as not improved actually was made worse, since he tolerated the medication poorly

Subsequent cortisone therapy produced remission in one patient who had had good response to ACTH (table 1) A second patient had a brief (3 week) remission with ACTH, and had some relief of pain from subsequent cortisone therapy Cortisone had essentially no effect in 2 other patients, neither of whom had had significant response to ACTH

DISCUSSION

ACTH administration produced clinical improvement comparable in quality but not in duration to that after cortisone therapy in 3 out of 8 patients Two of the 3 patients who had proof of the greatest adrenal stimulation had remission in spite of the concomitant rise in 17-ketosteroid excretion (and presumably similar rise in biologic androgens) which would be expected to exacerbate the disease It is felt, therefore, that this clinical improvement is due to the effect of the adrenal corticoids which are perforce released along with the androgens This in turn indicates that it is not adrenal suppression, but the direct action of the cortisone which produces the clinical changes with cortisone therapy of advanced prostatic carcinoma

Whether this cortisone effect works by an aspirin-like mechanism, or through euphoria, by a nonhormonal anti-inflammatory action, or by a hormonal shift cannot of course be firmly established from the data at hand The effect is too great for a simple "analgesic" reaction Euphoria was not noted clinically, but could have been present to a subclinical degree An effect on the connective tissue of a non-sex hormone type is possible, and would account for the decreased pain, but no change could be detected in the local lesion by palpation or in the metastases by x-ray

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POLYESTRADIOL PHOSPHATE FOR CARCINOMA OF THE PROSTATE A CLINICAL STUDY

C D GOODHOPE

Since Huggins stimulated interest in hormonal control of prostatic cancer, advance has been hampered by gaps in our basic knowledge of living cell physiopathology For no evident reason one prostatic tumor will remain localized for decades while another spreads rapidly in spite of intensive treatment Pathologists admit of an inability at times to distinguish normal from tumor cells Excellent urologists disagree on what constitutes adequate treatment While hormonal control of prostatic cancer is generally considered to be a real advance in treatment of this condition the type of estrogen used and mode of administration had not changed appreciably until Flocks[1] reported interesting results using the intravenous administration of diethylstilbesterol diphosphate Efforts to maintain adequate, constant therapeutic estrogen levels have not been successfully achieved over long periods on oral medication because of the unreliability of patients in self-medication and because of rapid excretion Ordinary depot substances have achieved little popularity due to individual intolerance and erratic absorption Intravenous administration is expensive and effective in maintaining levels only so long as administration continues Pellet implantation has not proven generally satisfactory

For the past year I have been using a new estrogenic substance, polyestradiol phosphate which is not a depot substance in the usual sense of the term, that is of remaining at the site of injection, but which makes possible the maintenance of a prolonged, constant therapeutic level by single monthly injections as far as this can be determined by urinary assays It is reasonable to hope that a substance of this type should act more physiologically since the amount of steroid contained in a steroid producing organ is usually small compared with that released over a period of time and it is generally believed, therefore, that there is a continuous release of steroids by the organ with but little storage If this be true, the best hormone therapy would appear to be one that simulates natural production and through the use of such a substance we could determine the effects of a constant sustained estrogen level in patients with prostatic carcinoma

The purpose of this preliminary report is to present some experience with this new estrogenic substance with new properties of prolonged action and possibly new modes of action, to describe the results seen after a year of treatment, and to speculate on the possible modes of action

Polyestradiol phosphate (P E P) is a stable, water soluble, white powder having a pH of 7 Its basic structure is the familiar steroid nucleus which, through a phosphorylation reaction, is made to form an extremely large molecular structure with a molecular weight of approximately 15000 as an upper limit The substance is then dialyzed to remove the lower molecular weight fraction It was

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Read at annual meeting of Western Section of American Urological Association, San Francisco Calif April 30–May 3 1956

[1] Flocks R H J Urol , 74 549, 1955

synthesized by the research laboratories of LEO in Helsingborg, Sweden.[2] It will be remembered that several structurally dissimilar phosphorylated substances are active antienzymes possibly with powers of influencing cell transport. Among some of these are[3] polyphloretin phosphate, phosphorylated hesperidin polyhesperetin phosphate, and polyphloroglucinol phosphate. P.E.P. is nontoxic in extremely large doses, 400 mg. have been given monthly to patients for a period of 12 months without evidence of liver damage or other toxic effects.[4] It has no estrogenic effect when taken orally.[5] Its fate, after intramuscular injection, has not been completely clarified. After intravenous injection radioactive phosphorus studies have demonstrated it to be rapidly bound in the reticulo-endothelial system as well as protein bound. Its fate after intramuscular injection must be somewhat different than after intravenous injection as its duration is approximately doubled. It is rapidly absorbed from the site of injection when given intramuscularly. P.E.P. escapes passage through the renal filter and is retained in the system, possibly because of the shape and size of the molecule. However,[6] after hydrolysis in the body, measurably increased amounts of estrogens are recoverable in the urine.

A series of 5 patients with proven carcinoma of the prostate of varying duration who had undergone orchiectomy and who had been on maintenance doses of 24 mg. TACE daily for varying periods, were maintained on monthly injections *of 40 mg.* of P.E.P. for a year after cessation of other estrogen therapy. Pain at the site of the injection was found in some cases for the first two or three injections subsiding thereafter, this was the only unpleasant manifestation. Clinical results were observed. In evaluating results, one must remember the desire of patients to recover especially when they know they are receiving a new drug. Prior to inauguration of treatment, therefore, the patients were informed that they were simply receiving a months' supply of the previous substance by injection.

COMMENT

The pharmacological properties of P.E.P. were studied. Five patients with proven prostatic carcinoma who had undergone orchiectomy and had been under treatment with 24 mg. TACE *daily* for varying periods of time were placed on 40 mg. of P.E.P. *monthly* for a year with cessation of other estrogen therapy. Their clinical progress was observed.

The following is a summary of our impressions.

P.E.P. 40 mg. when injected intramuscularly is capable of maintaining therapeutic estrogen levels for a month.[7, 8]

It has proven nontoxic in the cases studied.

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[2] Fernö, O., Fex, H., Högberg, B., Linderot, T. and Diczfalusy, E. In preparation.
[3] Beiler, J. M., Brendel, R. and Martin, G. J. J. Am. Phar. Assn. 43: 480–482, 1954.
[4] Diczfalusy, E., Fernö, O., Fex, H., Högberg, B., Linderot, T. and Rosenberg, T. Acta Scandinav. 7: 913–920, 1953.
[5] Notter, Gustaf. Stockholm, Sweden, unpublished data.
[6] Dicfalusy, E. Endocrinol., 54: 474, 1954.
Dicfalusy, E. and Westman, A. Acta Endocrinol., 21: 321, 1956.
[8] McDonald, Donald. University of Washington Medical School, unpublished research data.

Two patients with extensive metastases who appeared moribund at inauguration of treatment achieved remarkable remissions without change in their metastases After a year a clinical decline is again becoming evident The remaining cases demonstrate subjective and clinical benefits over that seen on previous therapy

A delay of 60 to 90 days is seen in some of the effects in some cases in the present treatment program

There are many facts we do not know about the salutary effects of estrogens in carcinoma of the prostate, however, if the apparent superior clinical benefits of P E P continue, attempts must be made to answer the following questions

1) Can the unusual therapeutic results be explained only on the basis of maintaining constant blood levels of estradiol or are they partly due to the anti-enzymatic effects of this phosphorylated high molecular substance? Are the effects due to altered cell transport, again a property of some phosphorylated substances? Is this substance and the substance used by Flocks similar in this respect? Is diethylstilbesterol diphosphate partly a diphosphate and partly a polyphosphate?

2) What is its effect on the pituitary-adrenal axis? Is the euphoria produced by a similar mechanism the same as that produced by cortisone?

3) Can beneficial results be maintained longer than those produced by other estrogen therapy?

4) Is there a direct stimulatory effect on the reticuloendothelial system?

5) How can the observed therapeutic "lag" period be explained? Can this be prevented by injections given at shorter intervals at inauguration of therapy?

It is unfortunate that more accurate biochemical studies of effectiveness are not as yet available This, however, being the case, the only remaining course is large scale, long term clinical trial

Acknowledgements 1) H Lundbeck and Company, Copenhagen, Denmark, LEO Pharmaceutical Company, Helsingborg, Sweden for a generous supply of P E P and use of unpublished research data, 2) Dr Egon Diczfalusy for unpublished research data, 3) Dr Donald F McDonald, University of Washington Medical School, for unpublished research data, 4) Dr Knute Berger for advice

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LACK OF CONVERSION *IN VIVO* OF Δ_4 ANDROSTENEDIONE-3,17 TO A MORE ACTIVE ANDROGEN BY PASSAGE THROUGH THE LIVER

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For a number of years this laboratory has been interested in androgens as they relate to prostatic growth, especially prostatic cancer, for we feel that the beneficial effects of castration for disseminated prostatic cancer result from the removal of testicular androgens The role of estrogens has been considerable but has not been investigated to any extent One probable explanation for relapse following castration is that androgen produced by the adrenals reactivates prostatic cancer

Based on measurement of total urinary 17-ketosteroids[1] (not biologically determined androgens), bilateral adrenalectomy prior to ready availability of cortisone was not feasible[2] With the availability of cortisone, bilateral adrenalectomy became practical,[3] but theoretically the beneficial effects observed could be ascribed to either adrenalectomy or cortisone

Based on experiments done here and elsewhere which suggested that the liver inactivates certain androgens,[4, 5] Grayhack and Harris devised a procedure in which, presumably, all adrenal effluent blood is first presented to the liver[6] It was thought that the advantages of this procedure over adrenalectomy which necessitated the administration of cortisone were that adrenal androgen might be inactivated by the liver, and yet the life sustaining hormone of the adrenal might not

Such considerations have prompted us to investigate the metabolism of a number of steroids, especially Δ_4 androstenedione-3,17, which Kochakian[7] showed

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* Trainee of National Cancer Institute at the time this work was done Present address 5th General Hospital Stuttgart, Germany

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Kochakian, C D A symposium on steroid hormones Univ of Wisc Press p 93, 1950

Two patients with extensive metastases who appeared moribund at inauguration of treatment achieved remarkable remissions without change in their metastases After a year a clinical decline is again becoming evident The remaining cases demonstrate subjective and clinical benefits over that seen on previous therapy

A delay of 60 to 90 days is seen in some of the effects in some cases in the present treatment program

There are many facts we do not know about the salutary effects of estrogens in carcinoma of the prostate, however, if the apparent superior clinical benefits of P E P continue, attempts must be made to answer the following questions

1) Can the unusual therapeutic results be explained only on the basis of maintaining constant blood levels of estradiol or are they partly due to the anti enzymatic effects of this phosphorylated high molecular substance? Are the effects due to altered cell transport, again a property of some phosphorylated substances? Is this substance and the substance used by Flocks similar in this respect? Is diethylstilbesterol diphosphate partly a diphosphate and partly a polyphosphate?

2) What is its effect on the pituitary-adrenal axis? Is the euphoria produced by a similar mechanism the same as that produced by cortisone?

3) Can beneficial results be maintained longer than those produced by other estrogen therapy?

4) Is there a direct stimulatory effect on the reticuloendothelial system?

5) How can the observed therapeutic "lag" period be explained? Can this be prevented by injections given at shorter intervals at inauguration of therapy?

It is unfortunate that more accurate biochemical studies of effectiveness are not as yet available This, however, being the case, the only remaining course is large scale, long term clinical trial

Acknowledgements 1) H Lundbeck and Company, Copenhagen, Denmark, LEO Pharmaceutical Company, Helsingborg, Sweden for a generous supply of P E P and use of unpublished research data, 2) Dr Egon Diczfalusy for unpublished research data, 3) Dr Donald F McDonald, University of Washington Medical School, for unpublished research data, 4) Dr Knute Berger for advice

1116 Summit Ave , Seattle 1, Wash

When Δ_4 androstenedione-3 17 was implanted in the spleen of castrate rats (group D) no prostatic growth was observed Whereas the amount of hormone absorbed was somewhat less in the spleen than from pellets in the skin we feel that these differences were not important When pellets were removed from each position it was clearly evident that pellets could be removed intact from the spleen and hence their weight could be determined accurately Subcutaneous pellets developed a fibrous covering which could not be removed entirely without fragmentation of the pellet with loss of hormone Furthermore the amount of hormone absorbed from intrasplenic pellets is greater than the amount necessary to induce rapid prostatic growth when placed subcutaneously

Bile duct ligation (group E and F) did not significantly alter the prostatic weight response to Δ_4 androstenedione-3 17 placed either subcutaneously or intrasplenically

These experiments indicate to us that when Δ_4 androstenedione-3 17 passes through the liver before entering the general circulation a more active androgen such as testosterone is not produced This is in contrast to the *in vitro* experiments of Kochakian which showed conversion of Δ_4 androstenedione-3 17 by liver slices[7]

It is possible that in those rats in which the bile duct was ligated more androgen reached the general circulation as evidenced by a slightly greater prostatic growth response (group E) In closing the enteral excretory pathway for steroids it is possible that the steroid content of the general circulation is increased

SUMMARY

Under the conditions of our experiments Δ_4 androstenedione-3 17 produces prostatic growth in the castrated rat when administered subcutaneously Such activity is abolished when this steroid is administered intrasplenically This is contrary to what might be expected from the observed conversion of Δ_4 androstenedione-3 17 to testosterone by liver *in vitro*

This work lends further credence to the belief that adrenal androgens as well as testicular androgens are inactivated by the liver *in vivo*

TABLE 1

Group	Bile duct ligation	Subcutaneous Δ_4 androstenedione 3,17 pellet implantation	Intrasplenic Δ_4 androstenedione 3,17 pellet implantation	Number of rats	Initial body weight grams	Final body weight, grams	Initial pellet weight mg	Amount of pellet absorbed mg	Total prostate weight mg
Stock diet intact									
A				5	305	329			692
Stock diet castrate									
B				6	297	313			52
C		Yes		10	292	314	32.3	10.0	274
D			Yes	9	294	297	32.0	4.8	47
E	Yes	Yes		12	294	285	31.9	7.6	296
F	Yes		Yes	11	286	270	31.6	3.6	55

was metabolized *in vitro* to testosterone by the liver, and which has been isolated both from adrenal tissue[8] and effluent adrenal blood.[9]

This study is concerned with the comparison of the prostatic growth stimulating properties of Δ_4 androstenedione-3,17 implanted in the form of pellets beneath the skin or in the spleen of castrate rats with and without interruption of the hepato-enteral circulation by bile duct ligation.

MATERIALS AND METHODS

The animals used were intact or castrate albino male Wistar rats which weighed approximately 200 gm. at the beginning of the experiment. These were divided into six groups as shown in table 1. Twenty-six days after castration, two pellets of Δ_4 androstenedione-3,17, weighing in the aggregate approximately 32 mg., were implanted through a number 11 gauge needle either subcutaneously (groups C and E), or into the spleen (groups D and F) of the castrate groups. At the time pellets were implanted, the common bile ducts were ligated in rats in groups E and F. Six days later all animals were weighed, killed with ether, and the dorsal and ventral prostates removed and weighed. At the same time the pellets of hormone were removed, dried, and weighed. All animals were examined to determine the presence of adhesions between the spleen and the parietal peritoneum. In one instance such adhesions were found and this animal was excluded from the experiment.

RESULTS AND DISCUSSION

The results are tabulated in table 1. Castrates receiving Δ_4 androstenedione-3,17 placed subcutaneously (group C) showed rapid prostatic growth. From similar experiments in this laboratory, the response observed was almost as great as when testosterone propionate was used as the androgen.[5]

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[8] Dorfman, R. I. Recent Progress in Hormone Research, 2: 179, 1948.

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ployed fearing damage to the urethra, perforation of the bladder or laceration of the hymen

Last year it occurred to us that perhaps small size instruments made on the standard French scale would help to allay the fear of both patients and parents

Through the kindness of Mr Frederick J Wallace of American Cystoscope Makers, Inc , a set of bougies of white polyvinyl impregnated with titanium were made (fig 1) They are a little more than six inches long, tappered and from 8 to 30F

They are short enough to be practically concealed within the hand, occupy little space in the catheter tray and do not seem to scare our female patients or the children's parents

We have used continuously for one year one set which has been always kept in either detergicide or cystan solutions without deterioration or alteration of its physical properties or qualities The construction is excellent because the instruments have not cracked or scaled as do silk woven bougies when left into cold sterilizing solutions for long periods of time

These bougies do not constitute a "must" in the urologist's instrument cabinet but may prove to be a convenient handy tool which we offer and present for your consideration

803 De Diego Ave , Santurce, Puerto Rico

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NEW FEMALE URETHRAL DILATING BOUGIES

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The presence of urethral strictures, chronic urethritis and contracted vesical necks in female patients is being recognized by the urologist and suspected by the general practitioner and gynecologist with greater frequency

When the surgical correction of vesical neck stenosis is not indicated urethral dilatations are the procedure of choice Also, the passage of sounds of variable caliber is one of the accepted procedures to treat chronic urethritis and urethro trigonitis

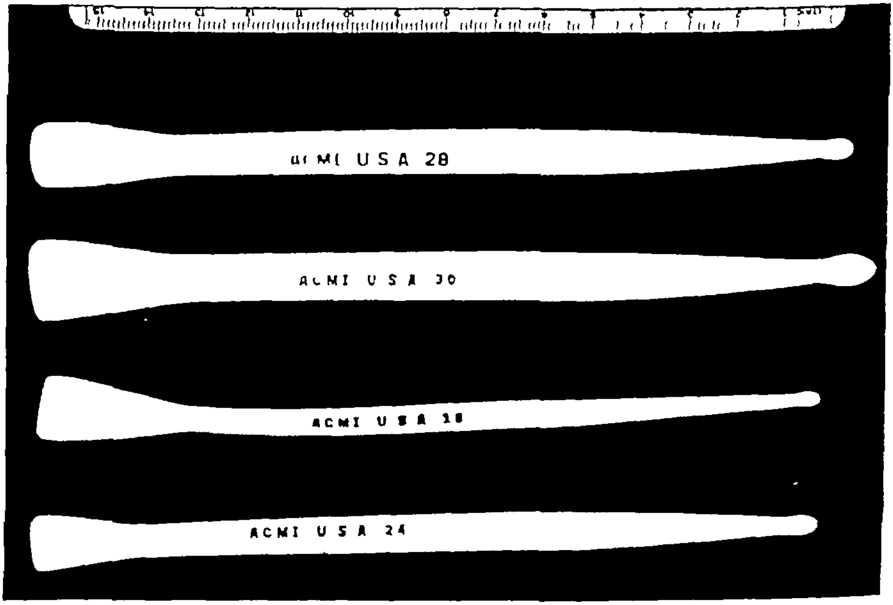

Fig 1 Polyvinyl titanium impregnated bougies

To dilate the female urethra we have used for several years the standard Le Fort, Benique sounds or silk-woven dilators currently used for male patients, but, because of its shortness, 1½ to 1¾ inches long, the female urethra only needs for adequate dilatation about 1/10 of the total length of the aforementioned instruments Furthermore, the curvature of the metal sounds produces some discomfort

On several occasions many nervous ladies have become frantic over the idea that such a large instrument is to be inserted into their urethras Also, since we became interested in pediatric urology many parents, who insist on being present during the examination or treatment of their children to avoid anxiety and fear of the infant, become greatly alarmed at the sight of the instrument to be em-

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two of lighter fluid is deposited to remove any dirt or old wax This is followed by the deposition of one drop of the mixture lighter fluid-wax and the parts worked several times to ensure a good penetration of the lubricant In a few minutes after evaporation of the solvent the instrument is ready for use Rarely if ever there is some excess of wax but if that is the case it can be easily removed with a piece of tissue paper and a toothpick

Since we began using this preparation our instruments are always ready for use Routinely we clean and lubricate all our instruments at one sitting approximately every three months We are satisfied with the results and wish to give this information to those confrères who might be interested in giving it a trial

303 de Diego Ave Santurce, Puerto Rico

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MAINTENANCE OF UROLOGIC ARMAMENTARIUM

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The great majority of the instruments used for urological diagnosis and treatment are of such mechanical precision that their construction requires much experience and a great deal of skill which adds immensely to their price value. Therefore, the urologist, nurses and personnel entrusted with cleaning and handling these instruments must and usually do exercise great care to avoid injuring the delicate lens system and the various component parts.

This presentation is limited to the movable parts of the various instruments at our disposal such as stopcocks, cystoscopic forceps, rongeurs, scissors locks and levels.

Like any piece of machinery the movable parts of our instruments suffer the inexorable effects of friction, oxidation and fair tear and wear. Adequate lubrication is required to ensure a smooth performance, reduction of friction and their sticking because of the effects of oxidation.

Often enough one finds a stopcock that freezes, or the working element of a resectoscope or a cystoscope does not move properly. Unless parts have been bent by injury the cause is obvious: lack of proper lubrication.

Beeswax is employed almost universally to maintain and insure proper lubrication of the moving parts of these instruments, the use of mineral or vegetable lubricants being inadvisable for obvious well known reasons.

In our experience however, the use of solid beeswax does not lubricate these instruments completely in many instances unless the wax is melted and this we have found to be time consuming.

It occurred to us some two years ago that if wax could be incorporated into a solvent, lamp threads could be made water tight and the stopcocks, latches, etc., lubricated more thoroughly without excessive deposition of wax and with great expedition of time.

After trying several solvents we found that benzene in the form of lighter fluid is ideal because wax is readily dissolved, and the fluid does not evaporate too rapidly which allows proper penetration into the inaccessible recesses of these parts.

Four to five cubic centimeters of lighter fluid to 1 gm. of wax has proved the most satisfactory proportion.

The results have been highly satisfactory. Frozen stopcocks and locks have been rendered serviceable, again avoiding the expense at the hands of the manufacturer or the annoyance of time lost during repairs.

To obtain the best results we proceed as follows: The moving parts are carefully washed with soap and water, dried and cleansed well with cotton swabs. Rust if present is removed with a toothpick or wood applicators. If necessary a drop or

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AORTOGRAPHY AND PNEUMOGRAPHY IN CHILDREN

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"Aortic injection in the young is today extremely difficult, dangerous and unsatisfactory—as yet the technique of its satisfactory administration in infants and children has not been perfected" These quotations from Campbell,[1] in reference to the intra-aortic injection of contrast medium for diagnostic arteriography, were, in 1951, probably representative of the opinions of many if not most, urologists

It is only within the past 10 years that translumbar aortography has been widely accepted and employed as an important adjunct to the basic procedures of urologic diagnosis Only now are sufficient data and experiences accumulating which permit recognition of the more specific indications for, and limitations and complications of diagnostic aortography There are of course, both enthusiastic proponents[2, 3] and critics[4, 5] of the technique and its application

Despite the increasing volume of literature concerning the use of aortography little is written, except individual case reports, relative to its use in children Those urologists[6-8] whose earlier papers did much to encourage the use of aortography made no specific mention of its application in infants or children Goodwin, Scardino and Scott[9] in 1950 mentioned the use of translumbar aortic puncture for arteriography in 5 children ranging from 18 months to 11 years of age with two failures due to inability to needle the small aorta At that time they said "We are not aware that aortograms have heretofore been made on such small children" Potts[10] reported attempting translumbar aortography on five children below the age of 12 years without success in any of the five though he obtained a satisfactory examination in one 13-year-old boy

Gammelgaard[11] reporting aortography in a 16-month-old female by direct femoral artery catheterization remarked, 'We had no experience in lumbar

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Read at annual meeting of Western Section of American Urological Association, San Francisco Calif April 30–May 3 1956

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[2] Smith P G , Rush T W and Evans, A T Evaluation of translumbar arteriography J Urol 65 911–921, 1951

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[9] Goodwin W E Scardino P L and Scott W W Translumbar aortic puncture and retrograde catheterization of the aorta in aortography and renal arteriography Ann Surg , 132 944–958 1950

[10] Potts I F Further experiences in aortography Med J Australia 1 232–233 1955

[11] Gammelgaard A Horse-shoe kidney in a child of 16 months elucidated aortographically Acta chir scand 107 163–169 1954

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AN IMPROVED URINAL FOR PARAPLEGICS

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From the U S Veterans Administration, (New York Regional Office), New York 1, New York

The improvised condom-coupled urinal worn by paraplegics is by no means a perfect surgical appliance despite its long popularity Condoms were never intended for such arduous performances and are too fragile, too expensive, and must be changed too frequently because of breakage Furthermore, no single satisfactory method which has proved acceptable to all patients has been discovered to attach them to the penis

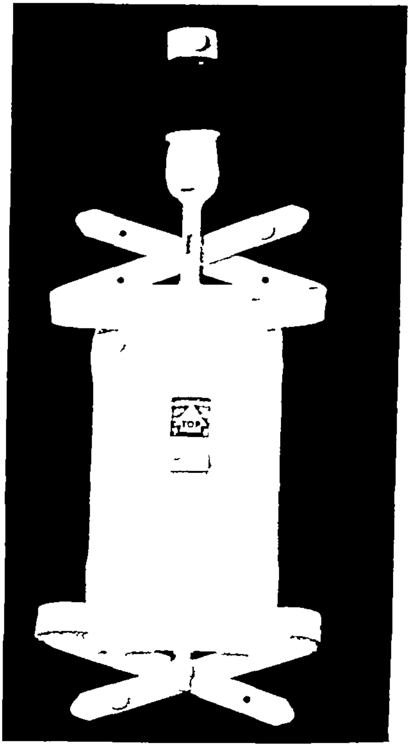

FIG 1

A new urinal for paraplegics is presented retaining the approved condom-coupled principle without any of its disadvantages As seen in the illustration, it consists of a strong plastic penile sheath coupled to a clean, lightweight plastic reservoir The penile sheath rolls on exactly like a condom and is firmly secured at the base of the penis by an adjustable, flat, elastic strap Two similar straps hold the reservoir to the thigh or leg as required To prevent urinary reflux, a flutter valve is located at the inflow of the reservoir A plastic tube may be attached to the outflow of the urinal for night drainage into a bedside bottle The reservoir and sheath may be obtained in any one of three convenient sizes Lukewarm water should be used for cleansing without adding soap or detergent

We are deeply grateful to C R Bard, Inc of Summit, N J for interest and assistance in developing this appliance and making it available

TECHNIQUE

We have previously reported on the details of the techniques we employ for aortography and pneumography[17] Preparation of the infant for the examination by aortography is the same as that for any roentgenographic, manipulative urologic procedure carried out under general anesthesia The use of general anesthesia in pediatric patients is essential in order to prevent unwanted movement Adequate x-ray facilities must be available A rapid cassette-changing device, or serial film-exposing device may be helpful but is not essential

Regardless of the patient's age or size, the basic anatomic landmarks for translumbar aortic puncture are the same With the patient in the prone position, the left twelfth rib is located and followed medially to its corresponding spinous process, which is marked For infants and small children, the lateral distance for insertion of the needle will obviously be less than the four fingerbreadths to the left of the midline, as advocated in adults However, since the aorta in the young lies nearer the midline, it is necessary for the aortographic needle to approach the vertebral column from a relatively more lateral position at a less acute angle in order to penetrate the aorta rather than pass anteriorly A point at, or just beyond, the left midlumbar position and just below the twelfth rib will ordinarily be satisfactory The size of the needle employed varies according to the patient's size, though the smallest used for the youngest patient was a 20 gauge, 3½ inch spinal needle The special 17 gauge, 7 inch needle with modified Huber tip, especially designed for translumbar aortography, may be used in older children

We have previously compared the use of the translumbar puncture and percutaneous femoral artery catheterization methods of aortography in adults[17] The percutaneous femoral artery catheterization technique may be employed in children of any age in whom the femoral artery is adequately large to permit easy puncture Reports in the literature[11, 13] indicate that, with rare exception,[13] in very small children femoral artery catheterization for aortography has more often been accomplished by surgical exposure We feel it is more expedient to use the translumbar approach, though if the adrenals are under study, the mobility of the catheter in the femoral technique may be advantageous

When the aorta has been punctured or catheterized a preliminary film is made after the rapid injection of 2 cc of contrast medium to check the position of the needle or polyethylene tubing The contrast medium may be any of those commonly used for intravenous urography We now believe that a 50 per cent solution of neo-iopax gives adequate contrast for good arteriograms and is as safe, or safer, than other agents The definitive arteriogram is made using a volume of contrast medium proportional to the patient's size Since abdominal aortography in adults requires only 10 cc to 15 cc of contrast medium the volume injected in infants and children has ranged from 4 cc to 10 cc While the child aortography and indeed this measure would hardly have been practicable with such small vessels " In a commentary on experience with 1500 lumbar aortographies, Parke G Smith[12] said, "We are not particularly happy with our experience in the use of this procedure in children, as it is extremely difficult to accomplish a satisfactory aortic puncture in the young " Snyder[13] commented regarding aortography in the young "The technique by direct paralumbar injection is not difficult in older children and adults, but in babies, because the aorta runs closer to the midline, we have preferred to cannulate the femoral artery from below " In a discussion of the age factor in translumbar aortography Maluf[3] wrote, "We do not like to inject children below the age of 10 because their aorta is quite narrow and tends to have its central axis more toward the midline This implies more lateral penetration through the body wall with the likelihood of entering stomach and/or pleura Furthermore, a more lateral approach may injure the thoracic lymphatic duct "

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[17] Walter, R C and Goodwin W E Aortography and retroperitoneal oxygen in urologic diagnosis a comparison of translumbar and percutaneous femoral methods of aortography J Urol, 70 526–537, 1953

[11] Hooks C A and Graves, O H Experiences with percutaneous transfemoral renal arteriography South Med J 45 587–590 1952

Notwithstanding these objections and reservations regarding the use of the translumbar technique for aortography in infants and children, we feel that, when indicated, the procedure is readily applicable despite early age and small size This opinion is upheld by the reports of Virenque and Parquie[14] and Fabre [15] They recognized that the aorta in infants and children is of small caliber in relation to the size of the vertebral body and lies relatively near the midline and that the lack of ossification in the vertebral bodies may make orientation of the needle point more difficult However, in their experience, aortic puncture was, as a rule, easily and simply done without complication even in the newborn Virenque and Parquie drew their conclusions from a series of 34 translumbar aortographic examinations in children less than 12 years of age, and Fabre, from a similar series of 62 cases There was no complication or ill effect encountered in either of these groups

The indications for the use of aortography in children are much the same as for adults Precise information valuable in the management of congenital anomalies of the upper urinary tract may be obtained by aortographic study This technique is also particularly useful in the examination of children with unexplained hypertension and in those suspected of adrenal tumor

It is in the delineation of the adrenal glands in cases of suspected tumor that retroperitoneal pneumography has its chief value in children Either aortography or retroperitoneal pneumography alone may positively locate an adrenal neoplasm prior to surgery, but in combination they produce an especially effective diagnostic study, as has been described elsewhere [16]

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[12] Smith, P G Résumé of experience in making 1,500 renal angiograms J Urol , 70 328–331, 1951

[13] Snyder, C H , Bost, R B and Platou, R V Hypertension in infancy with anomalous renal artery diagnosis by renal arteriography, apparent cure after nephrectomy Pediatrics, 15 88–92, 1955

[14] Virenque, J and Parquie, M L'Aortographie chez l'enfant Presse méd , 60 934–935, 1952

[15] Fabre, P L'Angiographie renale Trans Internat Soc Urol (Athens), 1955, vol 1, pp 348–392

[16] Goodwin, W E , Moore, E V and Peirce, E C II Roentgenographic visualization of adrenal glands Use of aortography and/or retroperitoneal pneumography to visualize adrenal glands, combined adrenalography J Urol , 74 231–242, 1955

TECHNIQUE

We have previously reported on the details of the techniques we employ for aortography and pneumography.[17] Preparation of the infant for the examination by aortography is the same as that for any roentgenographic, manipulative urologic procedure carried out under general anesthesia. The use of general anesthesia in pediatric patients is essential in order to prevent unwanted movement. Adequate x-ray facilities must be available. A rapid cassette-changing device, or serial film-exposing device may be helpful but is not essential.

Regardless of the patient's age or size, the basic anatomic landmarks for translumbar aortic puncture are the same. With the patient in the prone position, the left twelfth rib is located and followed medially to its corresponding spinous process, which is marked. For infants and small children, the lateral distance for insertion of the needle will obviously be less than the four fingerbreadths to the left of the midline, as advocated in adults. However, since the aorta in the young lies nearer the midline, it is necessary for the aortographic needle to approach the vertebral column from a relatively more lateral position at a less acute angle in order to penetrate the aorta rather than pass anteriorly. A point at, or just beyond, the left midlumbar position and just below the twelfth rib will ordinarily be satisfactory. The size of the needle employed varies according to the patient's size, though the smallest used for the youngest patient was a 20 gauge, 3½ inch spinal needle. The special 17 gauge, 7 inch needle with modified Huber tip, especially designed for translumbar aortography, may be used in older children.

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When the aorta has been punctured or catheterized a preliminary film is made after the rapid injection of 2 cc of contrast medium to check the position of the needle or polyethylene tubing. The contrast medium may be any of those commonly used for intravenous urography. We now believe that a 50 per cent solution of neo-iopax gives adequate contrast for good arteriograms and is as safe, or safer, than other agents. The definitive arteriogram is made using a volume of contrast medium proportional to the patient's size. Since abdominal aortography in adults requires only 10 cc to 15 cc of contrast medium the volume injected in infants and children has ranged from 4 cc to 10 cc. While the child aortography and indeed this measure would hardly have been practicable with such small vessels " In a commentary on experience with 1500 lumbar aortographies, Parke G Smith[12] said, "We are not particularly happy with our experience in the use of this procedure in children, as it is extremely difficult to accomplish a satisfactory aortic puncture in the young " Snyder[13] commented regarding aortography in the young "The technique by direct paralumbar injection is not difficult in older children and adults, but in babies, because the aorta runs closer to the midline, we have preferred to cannulate the femoral artery from below " In a discussion of the age factor in translumbar aortography Maluf[9] wrote, "We do not like to inject children below the age of 10 because their aorta is quite narrow and tends to have its central axis more toward the midline This implies more lateral penetration through the body wall with the likelihood of entering stomach and/or pleura Furthermore, a more lateral approach may injure the thoracic lymphatic duct "

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[17] Walter, R. C. and Goodwin, W. E. Aortography and retroperitoneal oxygen in urologic diagnosis: a comparison of translumbar and percutaneous femoral methods of aortography. J. Urol., 70: 526–537, 1953.

[18] Hooks, C. A. and Graves, O. H. Experiences with percutaneous transfemoral renal arteriography. South. Med. J., 45: 587–590, 1952.

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It is in the delineation of the adrenal glands in cases of suspected tumor that retroperitoneal pneumography has its chief value in children Either aortography or retroperitoneal pneumography alone may positively locate an adrenal neoplasm prior to surgery, but in combination they produce an especially effective diagnostic study, as has been described elsewhere[16] tract satisfactorily by intravenous urography Cystoscopy and retrograde pyelography indicated a normal appearing left upper urinary tract and a marked right hydronephrosis and hydroureter extending to the ureterovesical junction A translumbar aortogram showed a normal left renal blood supply and surprisingly little attenuation of the right renal blood supply No aberrant renal vessels were seen On the basis of the arteriogram and the findings at the time of surgery, ureteroplasty was performed instead of a nephroureterectomy

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[12] Smith, P G Résumé of experience in making 1,500 renal angiograms J Urol , 70 328–331, 1951

[13] Snyder, C H , Bost, R B and Platou, R V Hypertension in infancy with anomalous renal artery diagnosis by renal arteriography, apparent cure after nephrectomy Pediatrics, 15 88–92, 1955

[14] Virenque, J and Parquie, M L'Aortographie chez l'enfant Presse méd , 60 934–935, 1952

[15] Fabre, P L'Angiographie renale Trans Internat Soc Urol (Athens), 1955, vol 1, pp 348–392

[16] Goodwin, W E , Moore, E V and Peirce, E C II Roentgenographic visualization of adrenal glands Use of aortography and/or retroperitoneal pneumography to visualize adrenal glands, combined adrenalography J Urol , 74 231–242, 1955

COMPLICATIONS

In this small series we have observed no serious ill effects from aortography Landelius[19] reported the death of a 4-year-old girl following renal arteriography done by surgical exposure, direct puncture and catheterization of the right femoral artery The contrast medium used was 70 per cent umbradil, of which 2 cc were used for a preliminary film and 15 cc for the examination The child died in cardiac arrest 4 hours after the examination while under general anesthesia for sympathetic ganglion block to relieve spasm of the right femoral artery Autopsy study revealed renal changes of a chronic nature associated with previous pyelonephritis and fresh ones of a nephrotic type exactly resembling those produced experimentally in rabbits by injection of concentrated umbradil If this child had not died from the complications of anesthesia, her subsequent course might have been that of temporary renal impairment as described by Miller, Wylie and Hinman[20] in adults following aortography where large amounts of highly concentrated contrast medium were injected

With retroperitoneal pneumography two temporary reactions were noted In one case the use of an excessive amount of oxygen in an infant produced distress and a mild shock-like picture for a short time In another case oxygen diffused into the scrotum producing a balloon-like filling which appeared alarming but caused no damage

CONCLUSIONS

Judiciously applied, aortography is a technically feasible and diagnostically important addition to the urologic examination of infants and children

Aortography in children is especially important in evaluating congenital anomalies of renal vascularization, structure or position, the investigation of hypertension and the localization of adrenal tumors

Despite a divergence of opinion among those experienced in the use of aortography translumbar puncture of the aorta seems to be the most expedient means of employing aortography in infants and small children

The percutaneous femoral artery catheterization technique of aortography may be used in children and may be especially advantageous in study of the adrenals

Retroperitoneal pneumography has its greatest usefulness in children either alone or in combination with aortography in localization of adrenal tumors remains quiet under anesthesia, we do not withdraw the needle or the tubing from the aorta until the wet films have been viewed and the results accepted as satisfactory

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[19] Landelius L Death following renal arteriography in a child Acta chir scand , 109 469-472 1955

[20] Miller G M Wylie E J and Hinman F , Jr Renal complications from aortography Surgery 35 885-896 1954

The technique of presacral oxygen injection for retroperitoneal pneumography, as described by Rivas, is essentially the same in children as in adults The amount of oxygen injected should be proportionate to the child's size For small children 100 cc to 200 cc may suffice while in older children the amount may be increased to 200 cc or 300 cc of oxygen for each side It is usually easier to perform this procedure in children under general anesthesia though it may be accomplished under heavy sedation prior to the general anesthesia given for aortography

RESULTS

We have collected a series of 17 cases in which aortography was used 19 times in infants and children as an important addition to the usual urologic studies The translumbar technique was used 17 times, the percutaneous femoral method 2 times and pneumography was combined with aortography on 3 occasions

The youngest patient was 6 weeks of age and the oldest 12 years Seven of the children were 2½ years of age or younger and the remainder were distributed in the 6 to 12-year age group

The indication for aortography was, in 7 cases, the evaluation of congenital anomalies of the upper urinary tract Six children were studied because of hypertension either unexplained or in association with apparent urologic disease Four cases were of suspected adrenal tumor and two were examined for possible vascular disease unrelated to the urinary tract

In every instance the aortograms contributed positive evidence, duplicated by no other diagnostic test, which was important in arriving at a final diagnosis, making a decision as to the necessity for surgical intervention or indicating the kind of surgical management to be used

CASE REPORTS

Two abstracts of representative case histories are here presented as examples of the usefulness of aortography in pediatric urology

Case 1 R V , a 23-month-old white male with multiple, associated congenital anomalies including exstrophy of the bladder, epispadias, undescended testes and pelvic kidney, was hospitalized for evaluation and treatment Excretory urography showed a single pelvic kidney with moderate hydronephrosis and hydroureter Translumbar aortography demonstrated a single long renal artery, arising at the bifurcation of the aorta, that supplied the pelvic renal mass At surgery it was possible to mobilize the pelvic kidney and anchor it in a normal position in the left retroperitoneal area A sigmoid bladder was created and a ureterosigmoid anastomosis performed A postoperative translumbar aortogram showed the renal artery normally patent and uncompromised by the change of its course and position

Case 2 D E , a 6-month-old white female, was hospitalized for study because of recurrent urinary tract infection and inability to visualize the upper urinary

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PREOPERATIVE DIFFERENTIATION BETWEEN HYPERPLASIA AND TUMOR IN CUSHING'S SYNDROME

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The identification of the cause of Cushing's syndrome (hyperplasia, adenoma, or tumor) before operation allows a more direct surgical approach and permits the reasoned use of excision and hormones Our experience in 20 patients who came to surgery is reviewed for the value of hormonal stimulation and suppression tests and of x-ray procedures for differentiation between hyperplasia and tumor

THEORETIC CONSIDERATIONS

Overactivity of the adrenal gland may cause androgenic and anabolic changes (the so-called adrenogenital syndrome, and virilization) if the principal products are androgenic hormones, reflected in the excretion of urinary 17-ketosteroids (fig 1) On the other hand, the secretion may have an almost pure catabolic or nitrogen-wasting effect, resulting in the increased excretion of 17-hydroxycorticoids (Porter-Silber chromogens) Ordinarily, a mixture of anabolic and catabolic effects is found The tests of hormonal secretion assess approximately this relative increase of androgens and of corticoids

The excretion of anabolic-androgenic and catabolic hormones not only differentiates virilization from Cushing's syndrome, but also allows to some extent for the distinction between adrenal hyperplasia, adenoma, and carcinoma Roentgenography allows further distinction between hyperplasia on the one hand and adenoma and carcinoma on the other

The relative usefulness of these distinct approaches, hormonal excretion and x-ray signs, was evaluated in a series of 36 cases of Cushing's syndrome which have been studied at the University of California Medical Center, San Francisco, since 1952, at which time urinary 17-hydroxycorticoid excretion studies were first set up Twenty of these patients have come to operation and form the actual basis for our observations and conclusions

HORMONAL DIFFERENTIATION

Basal hormone studies Cushing's syndrome is suspected by clinical examination (table 1[1]), but requires substantiation by the laboratory An elevation of the basal determinations of 17-hydroxycorticoid (hydrocortisone and cortisone) and their inactive excretion products will strongly suggest abnormal activity of the adrenal cortex[2] A level above 12 mg /day of 17-hydroxycorticoids is suggestive, and higher levels are practically diagnostic[3, 5]

Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass June 4-6 1956

[1] Plotz, C M Knowlton, A I and Ragan, C The natural history of Cushing's syndrome Am J Med **13** 597, 1952

[2] Liddle G W Island D , Cornfield, J and Forsham, P H A clinically significant

SUMMARY

The experiences and opinions of several authors with reference to the use of diagnostic aortography in infants and children are presented

Modifications of technique in the application of aortography and retroperitoneal pneumography to children are discussed and possible complications are indicated Two illustrative case reports are included

The authors' conclusions are presented

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after ACTH stimulation and the weight of the gland(s) at operation gave an p of 0.12 (0.55 would be the 5 per cent probability level), indicating absence of correlation. However, only 14 cases were involved, and in several of these, only one gland was removed, so that total weight was estimated by doubling the weight of the single gland. That this method would not be entirely accurate is suggested by

TABLE 1. *Diagnostic and therapeutic procedures in Cushing's syndrome*

	Hyperplasia		Adenoma	Carcinoma
Signs & symptoms[1]	Obesity	97%	More rapid onset	Similar
	Hypertension	84.5		
	Oligomenorrhea—impotence in men	78.5		
	Hirsutism	71		
	Plethoric appearance	69.5		
	Weakness and backache	66.5		
	Purple striae	65.5		
	Acne, skin pigmentation, or other rash	54		
	Mental symptoms	49		
	Headache	46		
	Ankle edema	44		
	Purpura or easy bruisability	41.5		
	Poor wound healing or severe infection	36		
	Polydipsia or polyuria	32		
	Neurologic symptoms or signs	28		
	Virilism	7		
	Exophthalmos	7		
Hematologic data	Less than 50/cu mm		Similar	Similar
a. eosinophils	Less than 15% of total WBC			
b. lymphocytes				
Skull x ray	Hardly ever enlargement of the sella turcica. Osteoporosis with intact lamina dura		Similar	Similar
Glucose tolerance test	Diabetic curve		Similar	Similar
Hormone excretion	Moderately elevated		Slightly elevated and changing from day to day	Most elevated and fixed
a. 17 hydroxy corticoids	(Normal male 6-14 mg/24°) (Normal female 4-10 mg/24°)			
b. 17 keto steroids	Slightly elevated (Normal male 10-20 mg/24°) (Normal female 5-15 mg/24°)		Often low	Very greatly elevated
c. 8 hr ACTH test (20 u ACTH IV over 8 hrs)	Rise above 50 mg/day with normal 3-5 fold increase over baseline		Rise above 50 mg/day with greater than 5 fold increase over baseline	No rise

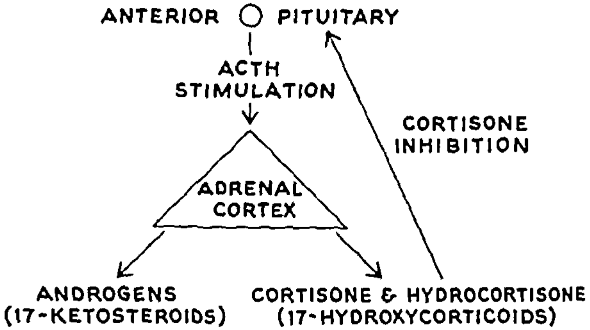
ANTERIOR PITUITARY
ACTH STIMULATION
CORTISONE INHIBITION
ADRENAL CORTEX
ANDROGENS (17-KETOSTEROIDS)
CORTISONE & HYDROCORTISONE (17-HYDROXYCORTICOIDS)

FIG. 1. Pituitary ACTH *stimulation of adrenal cortex* releases androgens and corticoids. Corticoids inhibit *further adrenal stimulation, and* so establish a balance.

Adrenal hyperplasia produced a significant increase in corticoid excretion in this series (mean level of 22 mg./day) and usually of the androgens as well (fig. 2). These levels are somewhat higher than that from adenomas (mean of 15.5 mg./day) which show a highly variable baseline characteristically. Thus two or three 24-hour collections should be obtained when in doubt. The highest basal levels were seen in 2 cases of cortical carcinoma (mean of 38.5 mg./day), and these proved to be extraordinarily stable. While the level in the individual patient may not necessarily be diagnostic because of variations from the mean which produce some overlapping, it usually is strongly suggestive.

ACTH stimulation test. Hyperplasia and adenoma, while abnormally active in hormonal secretion, are composed of essentially normal cells and so probably would *remain dependent to some extent on pituitary control* (fig. 1). The administration of pituitary adrenocortical stimulating hormone therefore should increase 17-hydroxycorticoid (and 17-ketosteroid) output. Carcinoma, on the other hand, its cells growing independently, would be expected to be unresponsive to ACTH stimulation.

The ACTH stimulation test has been standardized. 20 units of ACTH are given in slow intravenous drip over a period of 8 hours, and urine specimens are collected for the 24 hour period.[5] It is found that the normal adrenals showing a 3 to 5 fold increase over the baseline are rarely stimulated to excrete as much as 50 mg./day, whereas hyperplastic adrenals excrete more than this (fig. 2). The rise in 14 surgically proved cases was found to be from a mean resting level of 22 to a post-stimulation mean high of 70.6 mg./day. In 4 cases of adenoma, the rise definitely was greater (5 to 7 fold) to a mean level of 73.5 mg./day. *Carcinoma* produced no significant rise in corticoid excretion in our 2 cases (from 61 to 65, and from 16 to 19.5 mg./day).

Attempt at correlation between degree of rise in 17-hydroxycorticoid excretion

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steroidogenic assay of corticotropin (ACTH) administered extravascularly to human subjects *and to* guinea pigs. Endocrinol., **55**: 575, 1954.

[3] Forsham, P. H., Kolb, F. O., Liddle, G. W. and Island, D. Dynamics of adrenal cortical activation in different functional states. Am. J. Med., **17**: 108, 1954.

[4] Forsham, P. H. and Thorn, G. W. The adrenals. Chapter 4 in Williams, R. H., Textbook of Endocrinology. Philadelphia. W. B. Saunders Co., 1955.

[5] Laidlaw, J. C., Reddy, W. J., Jenkins, D., Abu Haydar, N., Renold, E. and Thorn, G. W. Advances in the diagnosis of altered states of adrenocortical function. New Eng. J. Med., **253**: 747, 1955.

after ACTH stimulation and the weight of the gland(s) at operation gave an r of 0.12 (0.55 would be the 5 per cent probability level) indicating absence of correlation. However, only 14 cases were involved, and in several of these, only one gland was removed, so that total weight was estimated by doubling the weight of the single gland. That this method would not be entirely accurate is suggested by

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TABLE 1 *Continued*

	Hyperplasia	Adenoma	Carcinoma
d 9 alpha fluorohydrocortisone suppression test 1 mg 9 alpha fluorohydrocortisone acetate (Squibb) for every 3 mg of urine 17 hydroxycorticoid, given in 4 divided doses q 6° p o for 3 days Urine collection on 3rd day	Hydroxycorticoids decreased 50% or more (unreliable)	*No change or* less than 50% suppression	*No change* (found rarely in fulminating bilateral hyperplasia)
Adrenal roentgenograms			
a Plain film	Adrenals can seldom be visualized	? Left renal displacement (15% lower)	Same
b I V urogram	Adrenals can seldom be visualized	Distinguish renal masses	Same
c Retroperitoneal oxygen insufflation (with tomograms)	*Bilateral* enlargement	Unilateral change, contralateral atrophy	Same or inability to penetrate affected side with oxygen

the appreciable differences in weights of the two glands in the same patient Absolute proof of the lack of correlation will come from a larger series of bilateral adrenalectomies

From the present data, it would appear that neither x-ray estimation of increased size nor operative determination of normal or increased weight can be used as a criterion of adrenal cortical function and corticoid activity A relatively small gland may have high hydrocortisone excretion and a larger one may have low excretion However, in only 1 case was the hormonally hyperactive gland as small as 5 gm, so that actual discrepancy between the hormonal diagnosis and the pathologic specimen was not large (table 2) If in addition one takes into account microscopic evidence of hyperactivity, the error is even less

Fluorocortisone suppression test[6] A very potent derivative of cortisone can be used for pituitary ACTH suppression The results are much less reliable, however, for Cushing's syndrome than for the syndromes of androgenic hypersecretion

9 α-fluorohydrocortisone acetate (Squibb) is given in the ratio of 1 mg for every 3 mg of basal 17-hydroxycorticoid excretion in the urine in 4 divided doses

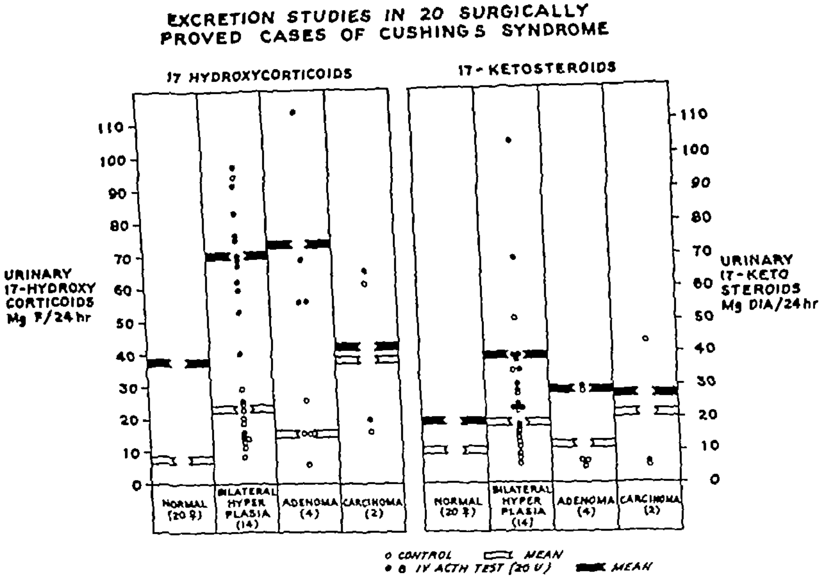

Fig 2 Baseline and stimulation levels of 17-hydroxycorticoid and 17 ketosteroid excretion in 20 surgically proved cases of Cushing's syndrome

Table 2 *Reliability of ACTH stimulation test in Cushing's syndrome* (20 cases, surgically verified)

	Total cases	Correctly diagnosed	Equivocal	Error
Hyperplasia or adenoma	18	17	1	0
Carcinoma	2	2	0	0

at 6 hour intervals each day for 3 days A 24-hour specimen of urine is collected on the third day for urinary 17-hydroxycorticoid and 17-ketosteroid determinations

Hyperplasia causing Cushing's syndrome may yield a 50 per cent or greater fall in corticoid excretion Adenoma may give no change at all, or a less than 50 per cent fall, and carcinoma, as would be expected, has shown no fall at all However, the results are so variable that the test is of greater theoretic than practical value in Cushing's syndrome This is in contrast to the findings in the adrenogenital syndrome[7]

EXCRETION STUDIES IN THREE ILLUSTRATIVE CASES OF HYPERPLASIA AND CARCINOMA

Hyperplasia The basal levels, and results of stimulation and suppression in a 24-year-old man with clinical Cushing's syndrome are shown in table 3 Bi-

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[6] Goldfein, A , Laidlaw, J C , Abu Haydar, N , Renold, A E and Thorn, G W Fluorohydrocortisone and chlorohydrocortisone, highly potent derivatives of compound F New Eng J Med , 252 415 1955

[7] Jailer, J W , Gold, J J and Wallace, E Z Evaluation of "cortisone test" as diagnostic aid in differentiating adrenal hyperplasia from adrenal neoplasia Am J Med , 16 340, 1954

TABLE 3 *24 hour urinary steroid studies*

T M male age 24 UCH 240340	Bilateral adrenal cortical hyperplasia	
	Total 17-OHC	17 KETOS
Control	29 mg F	50 mg DIA
ACTH stimulation	97 mg F	104 mg DIA
FF suppression	16 mg F	35 mg DIA

TABLE 4 *24 hour urinary steroid studies*

D D female age 62, UCH 49257	Adrenal cortical adenoma	
	Total 17-OHC	17 KETOS
Control	15 mg F	7 mg DIA
ACTH stimulation	113 mg F	22 mg DIA
FF suppression	8 mg F	4 mg DIA

TABLE 5 *24 hour urinary steroid studies*

E P male age 12 UCH 242287	Adrenal cortical adenocarcinoma	
	Total 17-OHC	17 KETOS
Control	16 mg F	5 mg DIA
ACTH stimulation	19 5 mg F	6 mg DIA
FF suppression	17 mg F	6 mg DIA

lateral hyperplastic adrenal glands were removed, and the patient has improved since operation

Adenoma Excretion studies on this 62-year-old woman with symptoms of Cushing's syndrome are shown in table 4

Operative removal of the adenoma after roentgen localization allowed the corticoid and 17-ketosteroid excretion to return to normal

Adenocarcinoma The findings in a 12-year-old boy with a 2-year history of arrested growth, obesity and hypertension are shown in table 5

Since the removal of the left adrenal including the 5 cm encapsulated carcinoma several months ago, he has required full maintenance on cortisone because of the extreme contralateral adrenal atrophy [8] [9]

ROENTGENOGRAPHIC DIFFERENTIATION

Radiologic techniques We have advocated a *plain film* coned-down over the adrenal areas[9] but we now find plain roentgenography to be rarely diagnostic in adrenal disorders Excretory urograms are only occasionally helpful in ruling out confusing renal masses, and retrograde pyelograms have been of no value

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[8] Goldberg, M B, Gordan, G S, Deamer, W C and Hinman F, Jr Mortality in surgically treated adrenocortical tumors I Report of 3 cases of Cushing's syndrome due to adrenocortical tumors Postgrad Med, 11 313, 1952

[9] Hinman, F, Jr and Forsham P H Adrenal surgery and its medical management, in Endocrinology in Clinical Practice, by G S Gordan and H Lisser, Year Book Publishers Chicago, 1953, pp 159–163

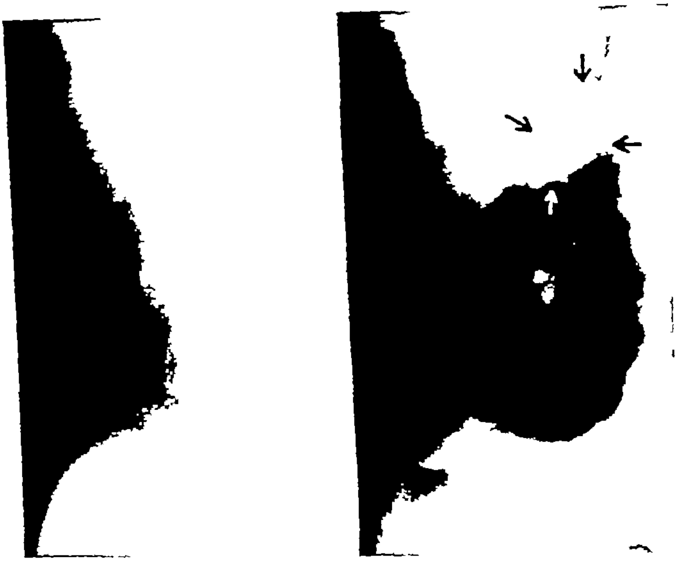

FIG 3 Poor visualization on excretory urogram but typical rounded contours on pneumogram of proved adenoma

TABLE 6 *Reliability of plain roentgenograms and presacral pneumograms in Cushing's syndrome (20 cases, proved surgically)*

	Total cases	Plain films			Presacral pneumograms		
		Diagnostic	No value	Error	Diagnostic	No value	Error
Normal size and hyperplasia	14	0	14	0	13	0	1
Adenoma	4	0	3*	1	4	0	0
Carcinoma	2	0	2	0	1	0	1

* Includes 1 case in which low left kidney suggested left tumor proved correct

In 14 cases of hyperplasia, in 3 of 4 cases of adenoma and in 2 cases of carcinoma, the state of the adrenals could not be distinguished on the plain films (fig 3, table 6) In one case of adenoma, the plain film actually indicated tumor on the opposite side In contrast, in another case of adrenal adenoma, the left kidney was displaced downward, which was interpreted as evidence of left adrenal tumor Such a tumor was confirmed by gas studies and removed at operation However, left renal displacement is not a reliable sign, since Rosenberg in an unpublished study from this hospital found the left kidney lower than the right in the abdominal films of 15 of 100 normal individuals [10]

Extraperitoneal pneumograms (presacral gas insufflation)[11] have proved most diagnostic especially when combined with tomography (fig 4, table 6) The value of tomography alone at the time of making the plain film has not been thoroughly

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[10] Rosenberg R H Personal communication

[11] Steinbach H L and Smith D R Extraperitoneal pneumography in diagnosis of retroperitoneal tumors A M A Arch Surg 70 161, 1955

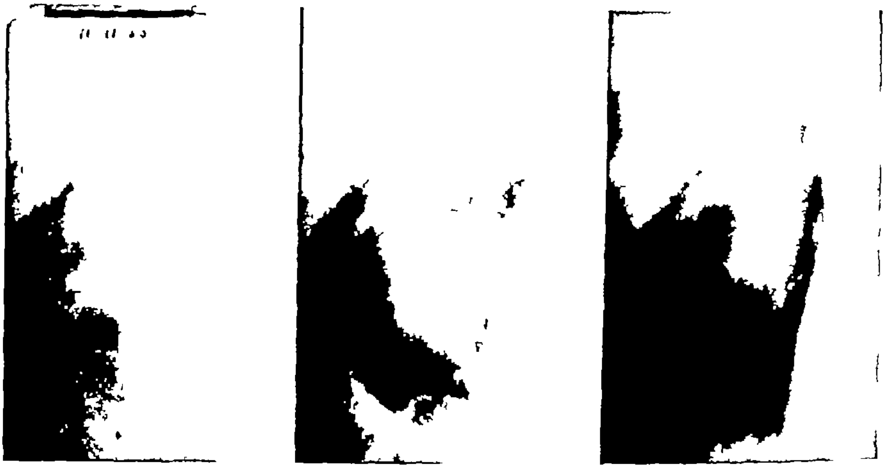

FIG 4 Nondiagnostic plain film, helpful pneumogram and diagnostic tomogram of functioning adrenal cortical carcinoma

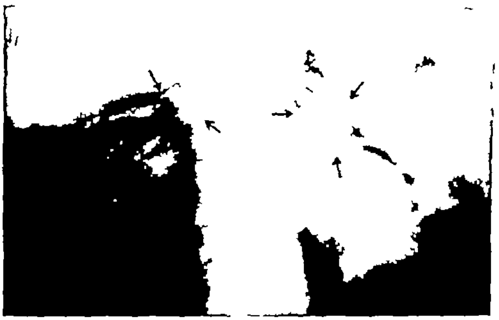

FIG 5 Apparent bilateral hyperplasia in patient with normal hormonal excretion (case excluded from present series)

studied, it may be that the perinephric fat will give adequate contrast in some cases without the confusing dissection produced by gas infiltration

As has already been pointed out, correlation would not be expected between the x-ray appearance of hyperplasia and the hormonal excretion, since there is no correlation between such excretion and the weight of the gland at operation (fig 5) However, as is shown in table 6, pneumograms are reasonably reliable if one groups normal-sized and hyperplastic glands together In other words, tumors were rarely found if the films showed normal or hyperplastic glands

The single serious error among the cases of hyperplasia was believed to be due to the presence of too much gas We read the films as showing a large left adrenal tumor and a small right adrenal gland (fig 6) Operation revealed bilateral hypertrophy (12 9 gm and 14 8 gm respectively)

Contralateral adrenal atrophy is a valuable sign of adrenal tumor (fig 7) However in the 1 case of carcinoma, the right adrenal appeared large by x-ray (the left was not adequately visualized) but was found atrophic on surgical exposure The tumor of course was then found on the opposite side Of equal value is the rounded contour of the typical adenoma or carcinoma (fig 3)

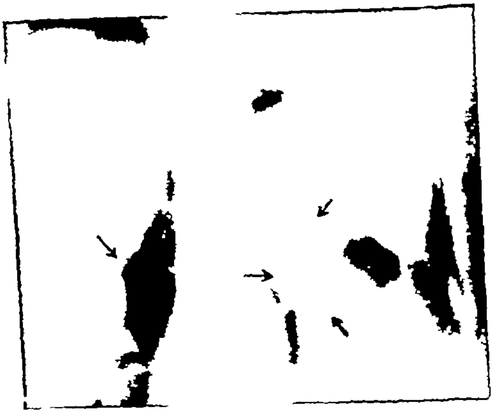

FIG 6 Error in reading of pneumogram apparent right adrenal atrophy with tumor on left side, proved to be bilateral hyperplasia

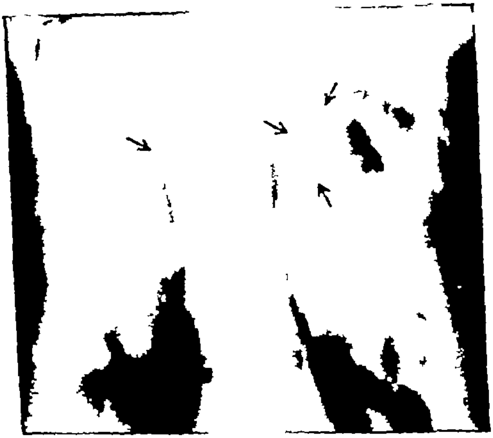

FIG 7 Typical pneumogram with tomography showing atrophic right adrenal and tumor on left

To *summarize* the roentgenographic data, the study of these films has shown certain criteria to be valuable even though our favorable experience with presacral pneumography is not shared by others[12]

First, a *rounded or oval mass* on the pneumograms is virtually diagnostic of adrenal neoplasm if corticoid excretion is elevated A large triangular adrenal associated with contralateral atrophy is also indicative of tumor Adrenal tumors do not lose their triangular shape until they are large In one case with normal 17-hydroxy corticoid excretion a mass considered by some but not all observers to be suprarenal proved to be a pancreatic cyst

Second, a very *small adrenal* is quite suggestive of neoplasm on the opposite side Among 6 cases (4 of adenoma and 2 of carcinoma), 4 appeared atrophic which was diagnostically helpful In the other 2, the small adrenal on the nontumorous side was not properly visualized because of inadequate distribution of gas However, in one of these last cases the tumor itself could be seen on the other side

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[12] Cope O and Raker J W Cushing's disease New Eng J Med 253 119 1955, ibid 253 165, 1955

Third, *displacement* of the left kidney below the level of the right kidney is an unreliable sign, since it occurs in 15 per cent of normal individuals

SUMMARY AND CONCLUSIONS

Hormonal excretion studies and roentgenograms were evaluated for their usefulness in distinguishing adrenal hyperplasia from adenoma and carcinoma in 20 cases of Cushing's syndrome coming to operation

Baseline determinations of 17-hydroxycorticoids and determinations after stimulation with ACTH in 14 cases of hyperplasia and 4 cases of adenoma showed that a resting level of over 12 mg /day was suggestive of Cushing's syndrome Post-stimulation levels of over 50 mg /day were diagnostic In 2 cases of carcinoma, stimulation produced no significant rise of the high basal 17-hydroxycorticoid level The 17-ketosteroid excretion was similarly recorded but alterations were of less magnitude and importance for the diagnosis of Cushing's syndrome than in syndromes consisting primarily of virilization

There was no correlation in this group between degree of maximal adrenal hyperactivity as measured by the stimulation tests and the size of the "hyperplastic" gland removed at operation This has significance for the urologist, since it suggests that he cannot predict adrenal cortical activity from the size of the adrenals either on pneumography or at operation The diagnosis of Cushing's syndrome therefore rests on clinical observations and steroid excretion studies

Suppression of 17-hydroxycorticoid excretion with 9-α-flourocortisone acetate was not helpful diagnostically, because of unpredictable variations

Plain roentgenograms were not helpful in differentiating hyperplasia from tumor, yet presacral pneumograms were diagnostic in all but 2 of 20 cases Of especial help was the observation of a rounded mass and the finding of contralateral adrenal atrophy

It is concluded that

Corticoid excretion after ACTH stimulation tests distinguishes a) normal adrenals from those producing Cushing's syndrome, b) adrenal hyperplasia and adenoma from carcinoma

Pneumograms, with tomography, distinguish hyperplasia from tumor

After using these diagnostic aids in combination, the urologic surgeon can subsequently operate with reasonable confidence of finding the expected adrenal lesion

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CLINICAL AND PATHOLOGICAL STUDY OF PYELONEPHRITIS IN PUERTO RICO. REVIEW OF 2,800 AUTOPSIES AND 1,887 CLINICAL RECORDS

LUIS A. SANJURJO AND ROBERTO F. FORTUÑO

From the Department of Surgery, Section of Urology, School of Medicine, University of Puerto Rico, San Juan, P. R.

A perusal of the medical literature discloses that the nonspecific infections of the kidney outrank in frequency the other known ailments affecting these organs. It is also evident that pyelonephritis must be considered a dangerous disease because of its peculiarity of going through periods of latency which vary from months to years. In other instances the disease remains unrecognized in view of the fact that its clinical manifestations may be minimal, not related to the urogenital system and sometimes not fully evaluated. Last but not least it is an unfortunate fact that the treatment of this disease very often is incomplete or inadequate, some patients time and again failing to recognize that repeated and careful followup studies are usually necessary and that if satisfactory results are to be expected and obtained, therapy must be prolonged. The resentment that many patients exhibit to the natural expense that results from the treatment of pyelonephritis is probably a contributory factor of great importance.

Most authors are in agreement that often enough the onset of pyelonephritis can be traced without difficulty to the period of early infancy or childhood, the disease manifesting itself in one way or another late in life after periods of latency. There is also enough evidence available to convince the most optimistic that pyelonephritis is sometimes an incurable disease, regardless of the zeal and interest exercised and directed towards obtaining a cure. The ultimate results among these patients are renal insufficiency with or without hypertension, uremia and death.

Found among patients of all ages, sex and race, pyelonephritis can usually be promptly diagnosed in the acute phase; when the disease has reached a chronic stage its recognition offers no great difficulties if a comprehensive urological survey is undertaken. Not infrequently the clinical picture and laboratory findings are misleading and one needs to exercise a great deal of ingenuity, intuition and painstaking efforts to establish a correct diagnosis. We agree with Taylor[1] that in these questionable cases empirical therapy should be carried out.

Until the discovery of the chemotherapeutic and antibiotic agents the treatment of the urinary tract infections, especially pyelonephritis, left much to be desired. Many patients so afflicted suffered for many years or died from the ravages of this disease. Undoubtedly we all have been witness in the past and occasionally nowadays of patients with pyelonephritis, acutely and desperately ill, some of them passing away while when by force we had to sit in silent impotence.

Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass., June 4-6, 1956.

[1] Taylor, R. D.: The diagnosis and treatment of pyelonephritis. Med. Clin. North Amer., 39: 957-963, 1955.

During the last two decades a score of new drugs has been added to our modern therapeutic armamentarium opening hence the path to bright avenues of hope in our dealings with urosepsis The therapeutic successes that are acknowledged and that were not seen in the past are many and if it is true that the overall picture and the fate of many patients suffering and doomed to die from pyelonephritis have been considerably changed for the better, it is indeed a sad reality that the natural immunity to these drugs observed in some bacterial strains and the resistance developed by others have curtailed and shadowed to a greater or lesser degree our initial optimism and expectations

Nesbit[2] has very wisely said that "An intelligent approach to the management of urinary tract infections at any age must therefore include a philosophy of therapeutic failure as well as success " In the light of present knowledge about this subject we must accept failures when they present themselves, but defeat should not be accepted until all the available means of examination and therapy are exhausted

How often are the resources at our disposal employed to their full capacity and how frequently is hope given up prematurely is hard to state and evaluate In the experience of all who have studied pyelonephritis one fact merits significant consideration, namely, that the rapidity of subsidence of the symptoms of acute pyelonephritis and of the exacerbations that are prone to occur during the chronic stage when treatment with chemotherapeutic or antibiotic agents is begun, has led many to be too optimistic about considering an infection cured when actually it was not This premature optimistic attitude, we believe, should be condemned because, as well as others who have studied and are interested in this subject, we have often observed among our patients that pyelonephritis is a disease difficult to cure

Wishing to evaluate the incidence of pyelonephritis in Puerto Rico and of determining what may be the prevailing successes and failures with the present day management of this disease, we decided to review the clinicopathological material on pyelonephritis at our disposal, this being the first study covering this subject to be carried out in Puerto Rico

PATHOLOGY

The presence of bacteria within the renal parenchyma is responsible in the early beginning for patchy areas of inflammation extending from the cortex to the medulla and renal pelvis Interstitial infiltration with inflammatory cellular elements, exudate and minute abscess formation are predominantly seen involving and producing damage to both elements of the nephron Upon healing, minimal scarring is observed but if not controlled, the infection progresses and with the appearance of new patches of infection further scarring results with additional destruction of the functional units of the kidney leading inexorably to the contracted pyelonephrotic kidney

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[2] Nesbit, R M Acute urinary tract infections in infants and children Ped Clin of North Amer , 2 771–779, 1955

TABLE 1 *Autopsies performed by the Department of Pathology, School of Medicine and Tropical Medicine, University of Puerto Rico incidence of pyelonephritis*

Year	Autopsies	Acute		Chronic		Acute & Chronic		With Nephrolithiasis	
		Case	%	Case	%	Case	%	Case	%
1926–1930	540	1	18	8	1 5	9	1 7	7	1 3
1931–1938	412	7	1 7	17	4 1	4	97	4	97
1939–1944	423	3	71	6	1 4	2	47	2	47
1945–1950	811	3	37	12	1 2	7	86	6	74
1951	614	2	32	12	1 9	12	1 9	5	81
Totals	2,800	16	57	55	2 0	34	1 2	24	86

ETIOLOGY

The presence of urinary calculi, urostasis, tumors, neurogenic dysfunctions of the urogenital tract and especially distant foci of infection are unquestionable factors that sooner or later permit bacteria to take a foothold in the renal parenchyma through various portals of entry, namely, the bloodstream, lymphatic passages, direct ascent through the ureteral lumen and lastly through a lymphohematogenous route

ANALYSIS OF PYELONEPHRITIS IN PUERTO RICO

The clinicopathological material used in this study consists of 2,800 consecutive autopsies performed at the School of Medicine and Tropical Medicine by the Department of Pathology under the direction of Dr Enrique Koppisch, professor of pathology Criminal and other medicolegal postmortem specimens examined by this department are not included in this report

This study also comprises a critical review of 1,887 consecutive personal private patients The information that follows, therefore, includes statistical data from 4 687 clinical records and autopsy protocols

POSTMORTEM ANALYSIS

In table 1 are found the distribution of autopsies per year group and the incidence of pyelonephritis in the acute and chronic stages

It is worthy of note in this table that pyelonephritis was complicated with renal lithiasis in 24 instances or 86 per cent of the protocols examined

In table 2 reference is made to the condensed total for all years, giving an overall incidence of 129 patients with pyelonephritis or 4 63 per cent It is also significant that pyelonephritis was considered the main cause of death in 23 instances only Our conclusions from this analysis are that the incidence of pyelonephritis in Puerto Rico is similar to that reported by Bell[3] in 1942 who found an incidence of 1 6 per cent of pyelonephritis in 33,360 autopsies Prewitt[4] also found 58 instances of pyelonephritis or 8 7 per cent in 667 autopsies and Staemm-

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[3] Bell, E T Exudative interstitial nephritis (pyelonephritis) Surg , 11 261, 1942

[4] Prewitt, G Pyelonephritis West J Surg , 51 393–450, 1943

TABLE 2 *Condensed total for all years*

Year	Total Post Mortems With Pyelonephritis	Pyelonephritis as Main Cause of Death
1926–1930	25 or 4 7%	10 or 1 8%
1931–1938	32 or 7 7%	5 or 1 2%
1939–1944	13 or 3 1%	0 or 0
1945–1950	28 or 3 2%	4 or 49%
1051	31 or 4 9%	4 or 65%
Total	129 or 4 6%	23 or 0 0078%

ler quoted by Lieberthal[5] encountered pyelonephritis in 58 or 4 8 per cent among 1,000 postmortem studies

PRIVATE PATIENTS

Race As the percentage of white private patients is higher than in the general population no significant conclusions can be revealed as to racial preponderance of pyelonephritis with this study

Age Pyelonephritis was significantly encountered in all age groups Detailed information on this topic is not included in this report because reference to age will be made in another publication which includes pyelonephritis in children

A diagnosis of pyelonephritis was made on 289 patients or 15 per cent, 191 or 66 per cent being women and 98 or 34 per cent men A diagnosis of acute pyelonephritis was made in 33 patients or 1 8 per cent The incidence, although apparently low, is explained on the basis that acute pyelonephritis is usually treated by the family physician, the general practitioner or the clinician, the urologist's assistance being sought, at least in Puerto Rico, when the infection persists and concomitant genitourinary disease is suspected The patients with acute pyelonephritis were seen during the first episode and the possibility of dealing with an exacerbation of an old process was carefully discarded as far as possible from the history In this group complete followup studies are available on 21 patients or 64 per cent, but in the remaining 12 or 26 per cent final studies were not possible because these patients either failed to return as soon as the acute symptoms subsided or perhaps medical advice and treatment were sought elsewhere

A complete cure was observed in 19 or 57 per cent of patients after obtaining repeated negative urine cultures, stained urine sediments and when the patients were free from urogenital or systemic complaints In two patients or 6 per cent the urinary infection persisted and passed into the chronic stage, the responsible organisms being Pseudomonas in one instance and E coli in the other

A diagnosis of chronic renal infection was made in 256 patients or 13 8 per cent The infection was limited to one kidney in 82 patients or 32 per cent while in the remaining 174 patients or 68 per cent both kidneys were considered to be involved upon finding positive urine cultures and Gram stains of the sediment of urine or when there was conclusive evidence of renal inflammation on pyelographic studies

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[5] Lieberthal, F Pyelonephritic contracture of kidney Surg, Gynec & Obst, **69** 159, 1939

The incidence of unilateral renal infection may appear too high but in this figure are included patients with unilateral renal lithiasis

Among the stone patients with infection 43 or 72 per cent were men and 17 or 28 per cent women In this group the ratio of infection is reversed this being explained by the fact that among our series of patients with stone the prevalence of calculi has been found to be greater in men than among women in a proportion of 3 1 In the review of this series of 1,887 patients renal calculi were found in 133 or 7 1 per cent, and as in 60 or 45 per cent of patients renal lithiasis and pyelonephritis were found concomitantly, this finding leads us to believe that, perhaps, in Puerto Rico renal infection may be a prominent contributing factor to stone formation

BACTERIOLOGY

Routine urine cultures and Gram stain studies of the urine sediments were done on all patients and sensitivity tests ordered only when indicated

Table 3 shows in order of frequency the various offending organisms isolated from the urine of 289 patients suffering from pyelonephritis Mixed infections were encountered in 36 instances or 12 per cent

In table 2 it is evident that Escherichia coli was the most prominent organism responsible for pyelonephritis Gram negative bacilli accounted for renal infections in 174 instances or 54 per cent against the cocci group which were isolated in 151 patients or 46 per cent

After this study was begun we thought that it might be of some interest to review the last 464 consecutive urine cultures with sensitivity tests done in our office

Of 454 urine cultures performed, 216 were found negative Many in this sterile urine group were followup studies of patients under treatment

In table 4 the various organisms isolated are shown in order of frequency, and

TABLE 3 *Bacteria isolated in 289 patients with pyelonephritis*

1 E coli	94
2 Non hemolytic Staphylococcus	38
3 Proteus	31
4 Alcaligenes faecalis	28
5 Non hemolytic Streptococcus	26
6 Hemolytic Staphylococcus	22
7 Pseudomonas	20
8 Aerobacter	18
9 Hemolytic Streptococcus	14
10 Staphylococcus albus	13
11 Paracolon	10
12 Alpha Streptococcus	10
13 Klebsiella	1
Total	325

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11	Paracolon	10
12	Alpha Streptococcus	10
13	Klebsiella	1
	Total	325

TABLE 4 *Organisms found in 454 consecutive urine cultures with sensitivity studies*

	Number	Pen	Erythro	Terra	Tetra	Aureo	Chloro	Strepto	Gantrisin	Fur	Resistant†
1 E coli	43	1	0	20	21	19	38	30	9	39	0
2 Alka faecalis	41	11	20	7	5	6	24	8	2	25	2
3 Streptococcus	34	5	22	6	7	7	20	8	2	20	1
4 B proteus	28	0	0	0	0	0	25	16	5	19	0
5 Paracolon	24	0	0	3	4	2	18	13	3	16	1
6 P aeruginosa*	21	0	0	0	0	0	5	11	0	5	8
7 Klebsiella	20	0	0	5	5	3	15	8	1	19	0
8 Staph albus	12	6	3	3	4	4	4	3	3	5	1
9 Staph aureus	12	12	4	2	1	1	7	5	0	9	0
10 Micro tetragenus	1	0	0	1	1	1	1	0	0	1	0
11 Yeast	2										
Total	238	35	49	47	48	43	157	102	25	158	13

Sterile urines—216
* Slightly susceptible
† Resistant to all tested drugs

the sensitivity to various drugs tested noted It is at once striking that furadantin and chloromycetin were the only two drugs to which most of the strains of bacteria isolated in culture media were sensitive, the third on the scale being streptomycin Interesting enough is the marked decrease in the incidence of sensitivity of the organisms identified to the other drugs tested Eight strains of Pseudomonas aeruginosa were found to be resistant to all tested drugs while in 13 other instances the bacteria were considered slightly susceptible to streptomycin, furadantin and chloromycetin

The use of chloromycetin in Puerto Rico has been greatly reduced as a result of the unfavorable reactions that have been reported during the last few years This in part may explain the lack of possible acquired resistance of bacteria to this drug In relation to streptomycin we are at a loss to explain the high incidence of sensitive strains inasmuch as the drug is used extensively in all medical circles for urinary and other septic conditions

We have had an excellent experience with furadantin * Most of the acute infections or exacerbations promptly subsided when the drug was administered and well tolerated by the patients

We have had very sad and regrettable experiences with polymixin B and as a result of this have excluded it from our therapeutic armamentarium using it only in extreme cases That is why we did not use it routinely in our sensitivity studies

SYMPTOMS

The symptoms of acute pyelonephritis are easy to recognize but during the chronic stage its manifestations may vary considerably (table 5) Although a combination of symptoms was often present among the patients studied the

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* Furadantin has been generously supplied to the Urology Service of the School of Medicine by the Eaton Laboratories, Norwich, Conn

TABLE 5 *Symptoms leading to a diagnosis of chronic pyelonephritis in 256 patients*

		%
1 Burning during urination	59	20 0
2 Microscopic pyuria	52	18 0
3 Microscopic hematuria	28	9 7
4 Acute renal colic	21	7 3
5 Lumbar pain dull in character	17	5 9
6 Chills and fever	17	5 9
7 Loss of weight and tiredness	12	4 1
8 Gross hematuria	10	3 4
9 Gross silent pyuria	8	2 8
10 Albuminuria	8	2 8
11 Lumbar and bladder pain	2	0 69
12 Blurred vision and fatigue	1	0 34

prominent and outstanding complaint was selected and noted in this table in order of frequency

Burning during urination and microscopic pyuria were the most frequent symptoms and findings leading to a diagnosis of pyelonephritis followed by microscopic hematuria The eight cases of chronic albuminuria were of interest because the diagnosis was established with the aid of the Addis count in all eight

Blurred vision and fatigue were the sole complaints of a 28-year-old woman without a previous history of any illness When referred to us she had moderate elevation of the blood pressure The Addis count was positive and pyelographic changes of pyelonephritis were evident Her phenolsulfonphthalein excretion was 1 8 per cent with 8 per cent of urea clearance The creatinine and blood urea nitrogen were 10 mg and 190 mg respectively Four years after establishing a diagnosis of pyelonephritis the patient died in uremia This case history is striking because the patient was in marked azotemia for several months and almost free of symptoms and furthermore, from the history, symptoms of urinary infection were not elicited

PERPETUATING FACTORS

In 160 patients, or 63 per cent, chronic pyelonephritis was unquestionably perpetuated by obstructive factors The 60 patients with renal or ureteral calculi are included among the obstructive factors In a forthcoming publication on the study of urinary lithiasis in Puerto Rico we shall attempt to establish a relation between lithiasis and infection, therefore the subject will not be discussed at present

In table 6 it is shown that among 256 patients with chronic pyelonephritis perpetuating factors were encountered in 252, or 98 per cent In four instances those conditions responsible for chronicity were not found Neither were they encountered in two of the acute cases

From these figures we conclude, therefore, that innumerable conditions of the genitourinary tract, congenital or acquired, if not promptly recognized and cor-

Table 6 *Factors responsible for chronicity in 252 patients*

		%
1 Renal calculi	60	21 0
2 Contracted vesical necks or median bars	46	16 0
3 Inadequate treatment	31	11 0
4 Urethrotrigonitis	25	8 6
5 Distant foci	19	6 5
6 Nephroptosis	18	6 2
7 Benign prostatic hypertrophy	17	5 9
8 Chronic prostatitis	5	1 7
9 Ureteropelvic obstructions without calculi	4	1 4
10 Carcinoma of prostate gland	4	1 4
11 Renal tumor	4	1 4
12 Ureteral stricture	4	1 4
a) Unilateral, 3		
b) Bilateral, 1		
13 Pyelogenous renal cysts	3	1 0
14 Urethral strictures	3	1 0
15 Stricture of the external meatus	3	1 0
16 Neurogenic bladder	2	0 69
a) Transection, 1		
b) Spina bifida, 1		
17 Polycystic kidneys	2	0 69
18 Contracted T B bladder (rt nephrectomy)	1	0 34
19 Ureterovesical fistula	1	0 34
Total	252	

rected will be responsible sooner or later for the development of infection which may become chronic

DIAGNOSIS

Without taking into consideration the source or reason whereby patients sought medical advice a complete urological examination was carried out This included history, physical examination, urine cultures, Gram stains, cystoscopy, pyelography (descending, ascending or both), renal function tests and the Addis count We are convinced that the Addis count is not only an extremely valuable adjunct to establish a diagnosis of chronic pyelonephritis but also a helpful index in determining therapy and prognosis

TREATMENT AND RESULTS

Nephrectomy proved to be a curative procedure in 19 patients or 32 per cent of the 60 cases with unilateral chronic renal infection The removal of renal or ureteral calculi in 27 patients resulted also in the sterilization of the urine In the remaining fourteen patients or 23 per cent, renal sepsis persisted requiring secondary nephrectomy in nine In 5 patients the renal function is stabilized but the infection persists These patients are under prolonged lifetime treatment, as advocated by Taylor

In the remaining 191 patients surgical intervention was necessary in 80 or 42 per cent An apparent cure of infection was obtained in 37 following therapy with antibiotics and chemotherapeutic agents for periods varying from one month to two and a half years

Of the remaining 112 patients eight died from their malignancy (4 kidney tumors and 4 carcinomas of the prostate) We have lost track of 93 patients

SUMMARY

Pyelonephritis is one of the most common diseases affecting the kidneys Although a rather silent disease its consequences may be disastrous if not adequately controlled Antibiotics have aided immensely in the treatment of urosepsis, but in spite of their use pyelonephritis continues to be a most difficult disease to control

An analysis of 4,687 clinical records and autopsy protocols was made to determine the incidence, etiology, clinical picture and complicating factors of pyelonephritis in Puerto Rico Detailed information on 352 urine cultures and bacterial sensitivity to different drugs was included

CONCLUSIONS

Histological evidence of pyelonephritis was found in 4 6 per cent of 2,800 autopsies

Pyelonephritis was found present in 15 per cent of 1,887 consecutive cases seen in our urological service

E coli continues to be the most common organism cultured from the genitourinary tract, but the incidence of bacteria of the cocci group seems to be definitely on the increase

The three most effective drugs as determined by bacterial sensitivity *in vitro* were furadantin, chloromycetin and streptomycin

Obstructive uropathies were by far the most common perpetuating factors found in our study but notwithstanding the beneficial effects of antibiotics, pyelonephritis continues to be a very difficult disease to control and eradicate

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AORTIC COMPRESSION IN THE MANAGEMENT OF MASSIVE HEMORRHAGE FROM THE RENAL ARTERY AT NEPHRECTOMY

REPORT OF A CASE

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Massive and sometimes uncontrolled hemorrhage from the renal artery is a problem faced by all urologic surgeons Its gravity is appreciated when the total renal blood flow of 1240 ml per minute is compared with the blood volume of 4500 ml in the normal person According to Best and Taylor, a rapid loss of 30 per cent of the blood volume without immediate replacement is lethal By simple calculation, it is seen that the operator has only a very short time to bring the renal artery under control in order to avoid a fatal outcome

The most common cause of uncontrolled bleeding at nephrectomy is the retraction of the artery, especially the left, at the time of its division or when the clamps are removed with the application of ligatures Avulsions of the renal artery from the aorta may occur in difficult mobilizations of the kidney as in the case of large renal tumors Much less commonly, bleeding is encountered from rupture of an arteriosclerotic vessel or aneurysm of the renal artery when clamps or ligatures are applied A rent in the vena cava is much more readily controlled

Of the methods used for recovering a bleeding artery, the simplest and best known is to grasp immediately the vessel with the fingers With this maneuver, the blinding flow is stopped, the wound can be evacuated of blood and blood clots, and the operator or his assistant is then given an opportunity to isolate and secure the vessel under direct vision Indiscriminate clamping in a bleeding wound is to be condemned as both ineffectual and likely to cause injury to adjacent structures Packing of the wound is helpful in low pressure bleeding from the renal vein or cava The usefulness of this procedure is limited in arterial hemorrhage because of bleeding into the pack Packing plus pressure can at times be of help in allowing the operator a brief interval to 1) organize his attack, 2) begin massive transfusion, 3) obtain, if needed, more adequate exposure, and 4) have special vascular instruments readied The operator is then able to utilize the method described by Rathbun of insinuating the fingers beneath the pack, palpating the aorta, and by moving caudally, grasp the renal artery at its origin

Scott and his group have described a case of massive bleeding from the right renal pedicle Hemorrhage was temporarily controlled by a gauze pack and pressure On the ninth postoperative day, the wound was opened and the pack slowly withdrawn Brisk bleeding occurred as the last of the pack was removed, and attempts to secure the pedicle were unsuccessful Therefore, the wound was repacked and closed On the eighteenth postoperative day, the patient suddenly began to hemorrhage into the pack, and went into profound shock The packing was reinforced and the vital signs stabilized by transfusion in preparation for

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass , June 4–6, 1956

surgery A transverse abdominal incision was made and the aorta approached through the lesser peritoneal sac By *manual compression of the aorta against* the spine, bleeding was controlled The right renal artery was identified and successfully ligated On the thirty-fourth day after his operation, the patient left the hospital

Recently we have encountered a situation in which bleeding from the left renal artery could only be controlled by aortic compression Our approach to the aorta was transthoracic This route was selected as the simplest and quickest for the patient in the decubitus position The following clinical report illustrates the usefulness of this maneuver

A G (G-NHH 43-18-71), a 68 year-old white man, was admitted on July 28, 1955, with a 1-year history of intermittent left flank pain accompanied by chills and fever Urologic workup disclosed calculus pyonephrosis on the left with complete loss of function and with physiologic compensatory hypertrophy in the right kidney as shown by differential phenolsulfonphthalein excretion On the following day, the left kidney was approached through the left flank, resecting the twelfth rib Endotracheal anesthesia was used The perirenal fat was indurated and adherent to the kidney Exposure of the pedicle following division of the ureter was tedious, owing to extensive acute and chronic inflammatory reaction When the pedicle was free, a No 2 chromic ligature was applied proximally, followed by application of three large Kelly clamps The pedicle was then transected between the second and third distal clamps and the kidney removed A suture ligature of No 2 chromic catgut was next placed through the pedicle As the ligature was being tied, even before the proximal clamp was loosened, there was a sudden gush of arterial blood into the wound The operator could neither feel the bleeding vessel nor evacuate blood from the wound quickly enough with the aspirator to visualize the point of hemorrhage The wound was then tightly packed, blood was ordered from the blood bank, an additional vein was cannulated, and massive transfusion was begun under pressure Despite the packing, the patient's blood pressure fell instantly to shock levels Two thousand cubic centimeters of whole blood rapidly administered failed to raise the blood pressure above 80 mm of Hg systolic A second attempt was made to locate the bleeding vessel, but this was thwarted by the rapid welling up of blood in the wound

The patient's blood pressure continued to fall Within a few moments the systolic pressure and pulse were unobtainable The patient's condition was desperate As repeated efforts to control hemorrhage through the flank had failed, it was decided to isolate and occlude the aorta above the renal artery in an area uninvolved in the dense perinephric phlegmon Dr W W L Glenn, chief of the cardiovascular section, was called and participated in gaining control of the bleeding renal artery He suggested that a transthoracic approach for compression of the aorta would be best Rather hastily, the incision was extended superiorly, the eleventh rib resected, and the pleura opened The aorta was identified by palpation and was slowly occluded by digital pressure Almost instantly, the brachial blood pressure rose, thus, at least temporarily, insuring cerebral oxygenation

The flank packing was slowly removed Gently the wound was evacuated of blood and clot Bleeding had stopped completely Then, as the tension was eased on the aorta, the operator was able to visualize and identify the renal artery It was apparent that the severely atheromatous vessel had been severed in tying the ligature An atraumatic, fabric-shod Crawford clamp was placed on the proximal portion of the artery while the distal end was oversewn with two layers of 5-0 arterial silk, care being taken to avoid further injury to the vessel The renal vein was next secured with two No 00 chromic ligatures and its clamps were removed Following the closure of the artery and continuation of the transfusion to 3000 cc, the patient's blood pressure returned to normal levels The incision was carefully closed in layers and the pleural cavity was drained with tube suction for 48 hours

The patient was discharged on the fourteenth postoperative day with wound completely healed The renal function showed 40 per cent output of phenolsulfonphthalein in 2 hours, the nonprotein nitrogen was 39, and the x-ray disclosed normal roentgenogram of the chest

SUMMARY

A technique is described by which massive bleeding from the left renal artery was controlled by immediate manual compression of the thoracic aorta The transthoracic approach for compression of the aorta is both rapid and easy, thus enabling the early recovery of the bleeding vessel and its ligation, and preventing an operative mortality In addition, it does not prolong the patient's hospitalization Furthermore, the utilization of the services of the vascular surgeon or his special instruments can prove of inestimable value to our specialty

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TWO RARE TUMORS OF THE RENAL PARENCHYMA

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Hamartomas and fibromas of the kidney are found occasionally at autopsy, but they are rarely diagnosed clinically or treated surgically. We have recently had the opportunity to study and treat two such patients with these tumors, and because of the rarity of such clinical reports, they are presented here.

CASE REPORTS

Case 1. A 12-year-old white child was admitted with the chief complaint of right flank pain which had been present 2 days. Her past health had been excellent, but 2 days prior to the onset of the flank pain, she was thrown against the horn of the saddle when her horse unexpectedly jumped a gate. There was a barely perceptible pain in the right upper quadrant of the abdomen until the onset of her acute flank pain which was severe and steady, being only partially relieved by 75 mg. demerol. Her temperature climbed to 103.6F and the pulse to 140 per minute. Upon examination, she appeared in extreme pain and the face was flushed, together with marked muscle guarding of the entire right flank and reduced excursion of the right diaphragm. No masses were palpable. The rectal and pelvic examinations were negative. The urine showed a specific gravity of 1.025, and was loaded with red blood cells, there were also 40 white blood cells per high dry field. Subsequent analyses showed similar findings. The admitting hematocrit was 37 mm. with a hemoglobin of 11.3 gm., and the total white cell count was 14,700 per cu. mm. An excretory urogram performed by the referring physician showed a constant, round filling defect 3 cm. in diameter (fig. 1). A retrograde pyelogram obtained the following day revealed moderate right hydronephrosis but the filling defect was less pronounced. Although the symptomatology and findings indicated a kidney lesion, medical consultation was held to rule out liver disease. When there was no improvement in her general condition, and after another 24 hours of observation, excretory urography was repeated, including lateral and oblique views, the same filling defect was found as in the initial studies. With this confirmation, a preoperative diagnosis of renal tumor with secondary hemorrhage was made and the child was operated upon the third hospital day. Using intratracheal anesthesia, a right flank incision, 15 cm. in length, was made over the tenth rib. This was resected intraperiosteally, thus opening the pleural cavity, the diaphragm was split for a distance of 5 cm. and the lower portion of the wound opened to the lateral border of the rectus abdominis muscle. This exposed a greatly enlarged kidney which filled the upper lateral one-half of the abdominal cavity, on the anteromedial aspect was a hematoma which measured approximately 6 cm. in diameter, this was adherent to necrotic and friable tissue which bled profusely but was controlled by packing. Initially

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[illegible] Then, as the tension was eased [illegible] and identify the renal artery [illegible] vessel had been severed in tying the ligature. A [illegible] Crawford clamp was placed on the proximal [illegible] artery [illegible] distal end was oversewn with two lines of 5-0 arterial silk [illegible] further injury to the vessel. The [illegible] No. 00 chromic ligatures and its clamps were removed. Following the closure of the artery and continuation of the transfusion to 3000 cc, the patient's blood pressure returned to normal levels. The incision was carefully closed in layers and the pleural cavity was drained with tube suction for 48 hours.

The patient was discharged on the fourteenth postoperative day with wound completely healed. The renal function showed 40 per cent output of phenolsulfonphthalein in 2 hours, the nonprotein nitrogen was 39, and the x-ray disclosed normal roentgenogram of the chest.

SUMMARY

A technique is described by which massive bleeding from the left renal artery was controlled by immediate manual compression of the thoracic aorta. The transthoracic approach for compression of the aorta is both rapid and easy, thus enabling the early recovery of the bleeding vessel and its ligation, and preventing an operative mortality. In addition it does not prolong the patient's hospitalization. Furthermore, the utilization of the services of the vascular surgeon or his special instruments can prove of inestimable value to our specialty.

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TWO RARE TUMORS OF THE RENAL PARENCHYMA

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Hamartomas and fibromas of the kidney are found occasionally at autopsy, but they are rarely diagnosed clinically or treated surgically We have recently had the opportunity to study and treat two such patients with these tumors, and because of the rarity of such clinical reports, they are presented here

CASE REPORTS

Case 1 A 12-year-old white child was admitted with the chief complaint of right flank pain which had been present 2 days Her past health had been excellent, but 2 days prior to the onset of the flank pain, she was thrown against the horn of the saddle when her horse unexpectedly jumped a gate There was a barely perceptible pain in the right upper quadrant of the abdomen until the onset of her acute flank pain which was severe and steady, being only partially relieved by 75 mg demerol Her temperature climbed to 103 6F and the pulse to 140 per minute Upon examination, she appeared in extreme pain and the face was flushed, together with marked muscle guarding of the entire right flank and reduced excursion of the right diaphragm No masses were palpable The rectal and pelvic examinations were negative The urine showed a specific gravity of 1 025, and was loaded with red blood cells, there were also 40 white blood cells per high dry field Subsequent analyses showed similar findings The admitting hematocrit was 37 mm with a hemoglobin of 11 3 gm, and the total white cell count was 14,700 per cu mm An excretory urogram performed by the referring physician showed a constant, round filling defect 3 cm in diameter (fig 1) A retrograde pyelogram obtained the following day revealed moderate right hydronephrosis but the filling defect was less pronounced Although the symptomatology and findings indicated a kidney lesion, medical consultation was held to rule out liver disease When there was no improvement in her general condition, and after another 24 hours of observation, excretory urography was repeated, including lateral and oblique views, the same filling defect was found as in the initial studies With this confirmation, a preoperative diagnosis of renal tumor with secondary hemorrhage was made and the child was operated upon the third hospital day Using intratracheal anesthesia, a right flank incision, 15 cm in length, was made over the tenth rib This was resected intraperiosteally, thus opening the pleural cavity, the diaphragm was split for a distance of 5 cm and the lower portion of the wound opened to the lateral border of the rectus abdominis muscle This exposed a greatly enlarged kidney which filled the upper lateral one-half of the abdominal cavity, on the anteromedial aspect was a hematoma which measured approximately 6 cm in diameter, this was adherent to necrotic and friable tissue which bled profusely but was controlled by packing Initially

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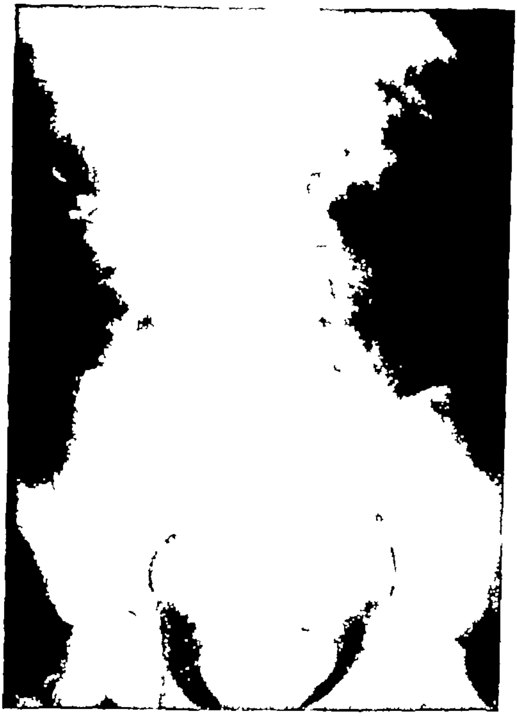


FIG 1 Excretory urogram showing persistent filling defect in right kidney caused by hamartoma

the mass was considered inoperable, as there was marked distortion of both the vena cava and aorta, but in carrying the dissection to the upper pole of the kidney, the pedicle was isolated without great difficulty The blood supply to the mass arose from the pedicle except for one large vessel which independently supplied the hematoma No further problem was involved in closing the wound, and a water seal was placed in the pleural cavity On pathological study, "the specimen consists of a kidney and tumor mass weighing 540 grams The kidney appears normal in size and shape and measures 13 by 6 by 5 5 cm , but protruding from the renal parenchyma is a large tumor mass two times as large as the kidney This is hemorrhagic and well encapsulated, it extends into and replaces the tissue of the renal pelvis with very little distortion of the actual renal architecture Upon section, the tumor appears lobulated and has a slightly yellow color and a granular consistency The intrapelvic portion has a complete capsule with no evidence of invasion of the renal substance " On microscopic study, "the renal parenchyma is essentially normal histologically The tumor is composed of two separate elements which are intermingled One is a rich vascular network of large, well-developed vessels, many of which are of the arterial type These show a periendotheliomatous proliferation of myeloblastic cells The stroma of the tumor is fat of the adult type with some interspersion of fetal type fat cells Diagnosis Angiomyolipoma of the kidney (hamartoma) "

The convalescence was uneventful and the patient was discharged on the seventh postoperative day Twenty-two months postoperatively the patient is in good health with normal hypertrophy and function of the remaining kidney The lung fields are clear and all tests for tuberculosis have been negative

Case 2 A 31-year-old white man was admitted with a chief complaint of right flank for 36 hours which began suddenly one night and radiated to the right lower quadrant The pain was severe and accompanied by nausea and vomiting, chills and fever He was observed for the possibility of a lesion in the abdomen requiring surgery, but the pain subsided in approximately four days and a mass in the right flank was then felt He was seen in consultation and excretory urograms were inconclusive, showing some deformity of the right kidney Eighteen months prior to admission, the patient was hospitalized 6 days because of a burning sensation in the right flank and the suspicion of infectious hepatitis The pain again appeared 2 months prior to admission but subsided spontaneously There were no urinary symptoms An appendectomy was done 6 months prior to admission, and the general health was fair, even though he was moderately under weight The physical examination showed a thin, young male, not acutely ill There was a poorly defined mass filling the right upper quadrant which moved sluggishly upon respiration and which was mildly tender There were discrete and small, shotty nodes in both inguinal regions, while the remainder of the physical examination was not contributory The urine was negative for albumin and sugar, the specific gravity was 1 017, and microscopic examination showed white blood cells with no red blood cells seen per high dry field The hemoglobin was 14 1 gm and a hematocrit on admission of 44 mm with no elevation of the white blood count A phenol red kidney function test showed good excretion of the dye in 1 hour with a good curve, and an excretory urogram showed a soft tissue mass 7 cm in diameter arising from the lower pole of the right kidney along its medial aspect This was divided from the renal shadow by an incisura of 1 cm while the function of both kidneys was good, but the right renal pelvis and the proximal portions of the lower calyces could not be visualized Apparently some compression was present, thus giving an impression of a large tumor mass Upon admission to the hospital the patient was resting comfortably, and the following day a combined excretory urogram and retroperitoneal air injection were performed (fig 2), as a retrograde pyelogram of the right kidney had been made prior to admission A diagnosis of a renal tumor was made and a nephrectomy accomplished the following day Under spinal anesthesia, a right flank incision was made over the twelfth rib Since the kidney lay high in the abdomen, the rib was resected without entering the pleural cavity, the kidney was readily visualized and appeared normal except for a large mass 9 cm in diameter which was light tan colored, and extending over the anterior surface were three large veins The kidney and mass were readily dissected down to the pedicle which was only moderately adherent On pathological study the specimen weighed 398 gm It was somewhat distorted in shape by a large tumor mass that occupied the lower medial pole This tumor was well circumscribed and measured 9 cm in its greatest diameter It was of cystic consistency on palpation, but upon sectioning it there was a solid tan color and finely granular consistency throughout Along

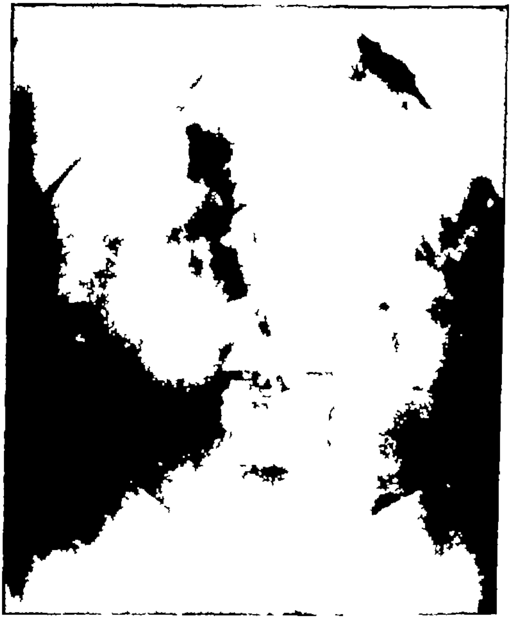


FIG 2 Combined excretory urogram and retrorectal oxygen insufflation showing space consuming lesion and tumor mass of fibroma

the lower pole were irregular areas of hemorrhagic necrosis involving about twenty per cent of the tumor mass The renal pelvis was distorted by the tumor with no invasion thereof, and the wall moved freely over the capsular surface The kidney otherwise appeared grossly normal and there was no involvement of the renal vein On microscopic study, the tumor was quite cellular and composed of spindle-shaped cells resembling fibroblasts There was no definite pattern and numerous small blood vessels were present There was some variation in nuclear size, but mitotic activity was not noted Because of the lack of invasive tendencies and absence of growth activity, it was felt that this will probably behave as a benign tumor Diagnosis "Fibroma of the kidney"

The convalescence was uneventful and the patient discharged on the fifth postoperative day Eighteen months postoperatively there is no local nor metastatic recurrence of the tumor

COMMENT

Hamartoma or angiomyolipoma is a rare tumor of benign character It is usually found at autopsy and frequently associated with sclerotic tuberculosis Approximately twenty cases have been reported to date at surgery and these tumors are seen mostly in the latter decades of life, the youngest case reported was 3 years of age In our case, this tumor was present without any evidence of associated sclerotic tuberculosis, and was of unusually large size, but typical in its gross and microscopic appearance (fig 3) showing three distinct tissue structures (adipose tissue, smooth muscle, and vascular elements) Fibroma of the kidney is exceedingly rare when seen of sufficient size to produce symptoms

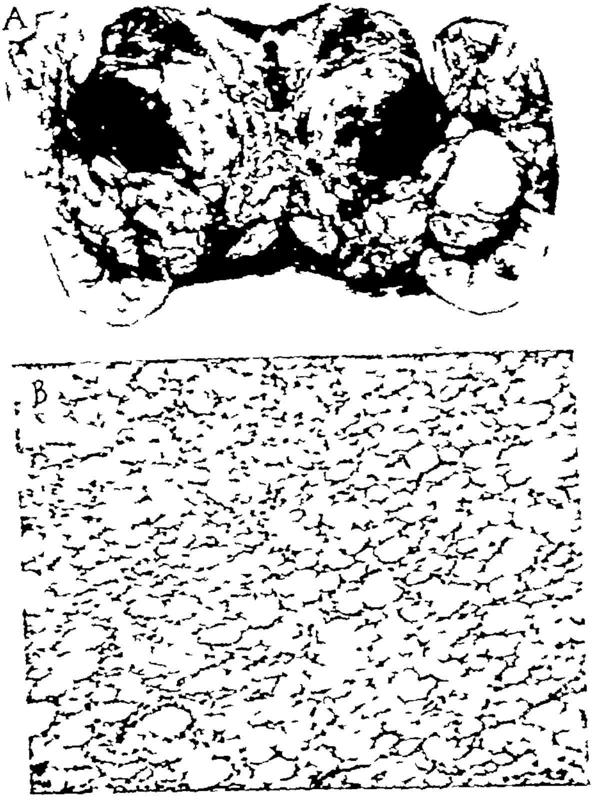
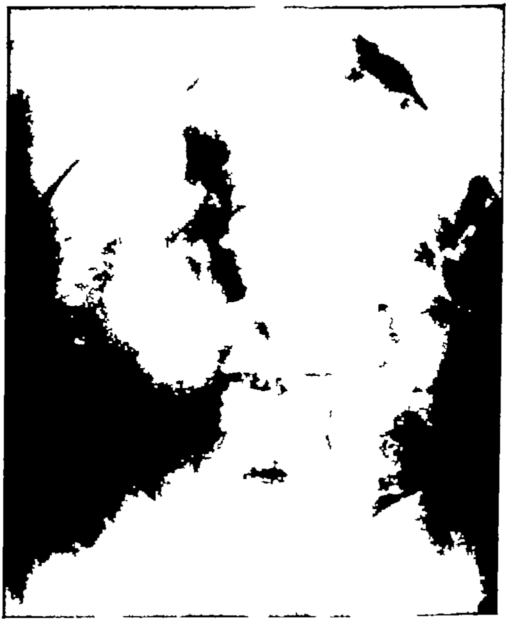


FIG 3 A, gross surgical specimen sagittal section, showing typical areas of adipose tissue and hemorrhage B photomicrograph with main constituents of angiomyolipoma

Kretschmer reviewed the literature in 1933 and found that 11 cases had been reported, in the past year, Chauvin reported a case of an enormous fibroma with an associated febrile response Fibromas of a few millimeters in diameter are often seen incidentally at necropsy, arising most commonly in the renal medulla In the second case, gross examination showed no definite capsule, as is usually seen in benign tumors but it otherwise had the typical appearance of a fibroma It is not particularly remarkable for its size alone, as one tumor from the renal parenchyma is reported by Gordon to have weighed 22 pounds, and tumors up to nearly 70 pounds have been reported in the perinephric tissue In fibromas, the microscopic picture is capable of wide variation from a dense sclerotic and hyalinized structure to that of loose edematous tissue even progressing to mucoid degeneration The presented case lies somewhere between the two extremes (fig 4) These two rare tumors are of interest for several reasons They both showed space-consuming lesions, and were diagnosed without difficulty as distortion was present and persistent upon pyelography It is interesting to note that only one of the tumors produced hematuria and pyuria, this, however, was more confusing than helpful and the insufflated oxygen in the retroperitoneal studies



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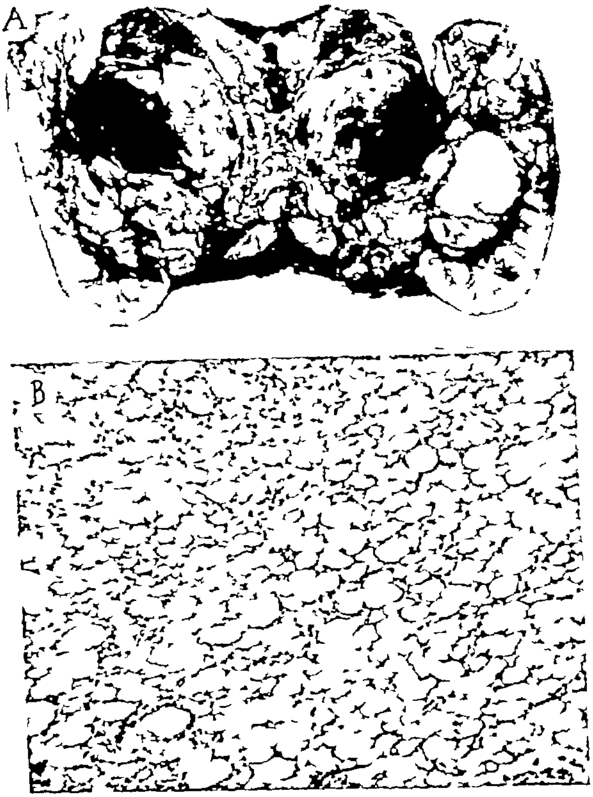

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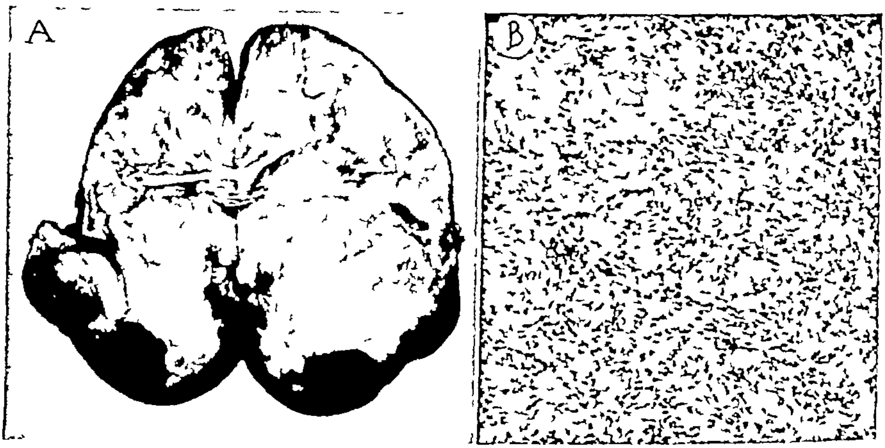

FIG 4 A, sagittal section through surgical specimen showing grossly homogeneous nature of tumor B, photomicrograph through tumor area which was composed almost entirely of fibrocytes

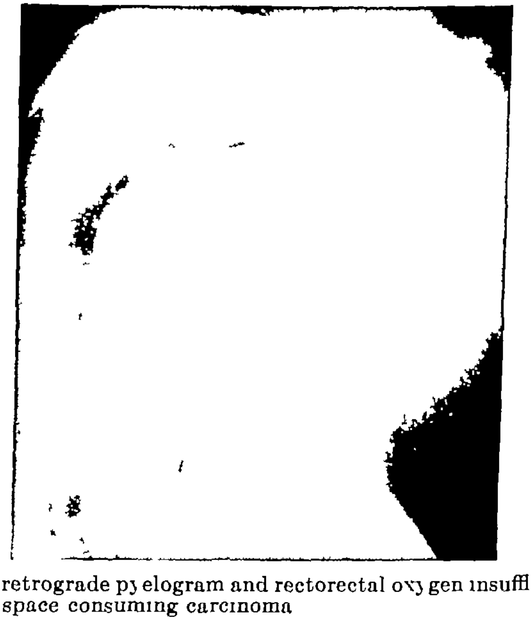

FIG 5 Combined retrograde pyelogram and rectorectal oxygen insufflation Lateral view gives full outline of space consuming carcinoma

diffused completely around the fibroma outlining it clearly In malignant tumors of this size, with extension to the surrounding tissue, the oxygen usually does not give a clear outline While this is a helpful observation, it cannot be considered a highly accurate adjunct to differential diagnosis between benign and malignant tumors of the kidney It is further noted that both of these tumors occurred in young people The hamartoma is the next to the youngest age on record (12 years) They both presented symptoms referable to a renal tumor, starting with flank pain of marked intensity which was typical of renal origin This pain was caused by hemorrhage into the tumor and immediate surrounding tissues, producing tension on the peri- and paranephric structures The differential diagnosis in both cases was between malignant tumor or benign cyst The most probable preoperative diagnosis in the 12-year-old child was an embryonal adenomyosarcoma (Wilms' tumor), but a diagnosis of a benign tumor was made preoperatively in the case of the fibroma A third patient not reported here, but 28 years of age, was seen with the history of left flank pain and intermittent hematuria for a duration of 18 months This was promptly diagnosed a benign tumor particularly when a large mass was palpated and an irregular filling defect was seen upon retrograde pyelography (fig 5) This proved to be a clear-cell carcinoma of the renal parenchyma with no gross evidence of metastases

SUMMARY

A case of angioliomyoma (hamartoma) of the kidney is presented in a 12-year-old girl, and one of a large fibroma of the kidney is reported in a 33-year-old man These cases are of interest because of 1) the rarity of both tumors, 2) the youth of both patients, particularly the one with the hamartoma, and 3) the fact that tumor was diagnosed preoperatively and a surgical specimen obtained in each case

The literature has been reviewed and these 2 cases are considered worthy of addition

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RESULTS OF NEPHRECTOMY IN HYPERTENSIVE PATIENTS

GERSHOM J THOMPSON

From the Section of Urology, Mayo Clinic and Mayo Foundation, Rochester, Minn

Since Butler's[1] original article (1937) describing excellent reduction of hypertension by excision of an atrophied kidney, many papers on this subject have appeared One of the early studies was that of Barker and Walters,[2] who detailed the results in 5 cases observed at the Mayo Clinic More recently, Barker[3] outlined the results of surgical treatment for unilateral renal disease in 100 patients who had hypertension and stated that the results 2 or more years after nephrectomy were good in 45 per cent, fair in 19 per cent and poor in 27 per cent, 9 per cent of the patients had died Braasch[4, 5] also has written on this subject

Smith,[6] in 1948, reviewed the literature up to that time and presented an analysis of 242 cases reported by various authors He concluded that good results had been obtained in only 19 per cent of all cases in which unilateral nephrectomy had been performed in the hope of permanently reducing hypertension He expressed the view that conclusions regarding good effects could not be drawn until the patient had been followed for at least 1 year, during which time the blood pressure should remain at or below a level of 140 mm of mercury systolic and 90 diastolic

While one might speculate how one can select the particular patients who will be improved by nephrectomy so that useless operation can be avoided in others, no data exist that will provide reliable answers Schroeder and Fish,[7] in 1940, suggested the criteria of recent onset of hypertension, unilateral renal involvement with diminished renal function, normal function in the other kidney, absence of retinitis and the presence of a persistently increased blood pressure To these criteria Perlmutter and Hermann[8] suggested adding that the kidney to be removed should be greatly reduced in size Some years ago, as a co-author with Pearman and Allen, I[9] made the statement that, "Statistical studies deal-

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ing with the question of relationship of renal disease to hypertension are likely to be misleading In our estimation, the question can be answered accurately in one way only by determining the effect on hypertension of removal of surgical lesions of kidneys"

PRESENT STUDY

The present article gives data concerning a consecutive series of cases observed at the Mayo Clinic from 1940 through 1954 It includes some of Barker's cases but not the earliest ones In addition to the effects following removal of atrophic kidneys, the effects of nephrectomy done for hypertensive patients with a variety of other renal diseases will be summarized

Almost 3,000 patients were subjected to unilateral nephrectomy at the clinic during the 15-year period just mentioned A diagnosis of hypertension was made preoperatively in 344 (about 11 per cent) The records of these patients were studied For several reasons, 7 patients were not included in the study

Of the 337 remaining patients (194 females and 143 males) who were subjected to nephrectomy, 39 had renal tumors, each of 119 had a kidney that either was atrophied or hypoplastic and the remaining 179 had various renal conditions, such as hydronephrosis, tuberculosis, calcareous pyelonephritis, including staghorn calculus, renal cysts (but not congenital polycystic disease), pyonephrosis, subcapsular calcified hematoma and aneurysm of the renal artery

The diagnosis of hypertension in these cases was made by an internist after complete study Hypertension was recorded as mild in some cases but in the large majority it was moderate and sometimes severe in character No case in which the diagnosis was questionable has been included

In determining the results after nephrectomy, the opinion as to the effect on the patient's blood pressure in the majority of cases was that expressed in the records by both internists and surgeons at the time they had charge of the patient

A large majority of the patients who were thought to have obtained a good effect were re-examined some years later at the clinic and the determinations of blood pressure often were made by the same physician who examined them preoperatively

In determining the results of surgical treatment, a good early effect does not mean that the blood pressure merely decreased 40 or 50 mm of mercury from extremely high levels and remained above 140 mm systolic, it means, on the contrary, that the pressure leveled off at values less than 140/90 and stayed there until the patient had recovered from the operation, had left the hospital and was dismissed from the clinic Good late effects were listed according to Smith's definition, the blood pressure in these patients remained at a level below 140/90 for more than a year and in some instances up to 14 years after operation

RESULTS

Of the 39 patients with tumors, 34 had hypernephromas, four had epitheliomas of the renal pelvis and one had an encapsulated neurofibroma A good early

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PRESENT STUDY

The present article gives data concerning a consecutive series of cases observed at the Mayo Clinic from 1940 through 1954 It includes some of Barker's cases but not the earliest ones In addition to the effects following removal of atrophic kidneys, the effects of nephrectomy done for hypertensive patients with a variety of other renal diseases will be summarized

Almost 3,000 patients were subjected to unilateral nephrectomy at the clinic during the 15-year period just mentioned A diagnosis of hypertension was made preoperatively in 344 (about 11 per cent) The records of these patients were studied For several reasons, 7 patients were not included in the study

Of the 337 remaining patients (194 females and 143 males) who were subjected to nephrectomy, 39 had renal tumors, each of 119 had a kidney that either was atrophied or hypoplastic and the remaining 179 had various renal conditions, such as hydronephrosis, tuberculosis, calcareous pyelonephritis including staghorn calculus, renal cysts (but not congenital polycystic disease), pyonephrosis, subcapsular calcified hematoma and aneurysm of the renal artery

The diagnosis of hypertension in these cases was made by an internist after complete study Hypertension was recorded as mild in some cases but in the large majority it was moderate and sometimes severe in character No case in which the diagnosis was questionable has been included

In determining the results after nephrectomy, the opinion as to the effect on the patient's blood pressure in the majority of cases was that expressed in the records by both internists and surgeons at the time they had charge of the patient

A large majority of the patients who were thought to have obtained a good effect were re-examined some years later at the clinic and the determinations of blood pressure often were made by the same physician who examined them preoperatively

In determining the results of surgical treatment, a good early effect does not mean that the blood pressure merely decreased 40 or 50 mm of mercury from extremely high levels and remained above 140 mm systolic, it means, on the contrary that the pressure leveled off at values less than 140/90 and stayed there until the patient had recovered from the operation had left the hospital and was dismissed from the clinic Good late effects were listed according to Smith's definition the blood pressure in these patients remained at a level below 140/90 for more than a year and in some instances up to 14 years after operation

RESULTS

Of the 39 patients with tumors, 34 had hypernephromas, four had epitheliomas of the renal pelvis and one had an encapsulated neurofibroma A good early

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RESULTS OF NEPHRECTOMY IN HYPERTENSIVE PATIENTS

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From the Section of Urology, Mayo Clinic and Mayo Foundation, Rochester, Minn

Since Butler's[1] original article (1937) describing excellent reduction of hypertension by excision of an atrophied kidney, many papers on this subject have appeared One of the early studies was that of Barker and Walters,[2] who detailed the results in 5 cases observed at the Mayo Clinic More recently, Barker[3] outlined the results of surgical treatment for unilateral renal disease in 100 patients who had hypertension and stated that the results 2 or more years after nephrectomy were good in 45 per cent, fair in 19 per cent and poor in 27 per cent, 9 per cent of the patients had died Braasch[4, 5] also has written on this subject

Smith,[6] in 1948, reviewed the literature up to that time and presented an analysis of 242 cases reported by various authors He concluded that good results had been obtained in only 19 per cent of all cases in which unilateral nephrectomy had been performed in the hope of permanently reducing hypertension He expressed the view that conclusions regarding good effects could not be drawn until the patient had been followed for at least 1 year, during which time the blood pressure should remain at or below a level of 140 mm of mercury systolic and 90 diastolic

While one might speculate how one can select the particular patients who will be improved by nephrectomy so that useless operation can be avoided in others, no data exist that will provide reliable answers Schroeder and Fish,[7] in 1940, suggested the criteria of recent onset of hypertension, unilateral renal involvement with diminished renal function, normal function in the other kidney, absence of retinitis and the presence of a persistently increased blood pressure To these criteria Perlmutter and Hermann[8] suggested adding that the kidney to be removed should be greatly reduced in size Some years ago, as a co-author with Pearman and Allen, I[9] made the statement that, "Statistical studies deal

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass , June 4–6, 1956

[1] Butler, A M Chronic pyelonephritis and arterial hypertension J Clin Invest , 16 889–897, 1937

[2] Barker, N W and Walters, Waltman Hypertension and chronic atrophic pyelonephritis—Results of nephrectomy J A M A , 115 912–916, 1940

[3] Barker, N W Hypertension and unilateral renal disease M Clin North Amer , 35 1041 1050, 1951

[4] Braasch, W F The surgical kidney as an etiologic factor in hypertension Canad M A J , 44 9–15, 1942

[5] Braasch, W F End results following nephrectomy in patients with hypertension J Urol , 68 6–10, 1952

[6] Smith, H W Hypertension and urologic disease Am J Med , 4 724–743, 1948

[7] Schroeder, H A and Fish, G W Studies on "essential" hypertension III The effect of nephrectomy upon hypertension associated with organic renal disease Am J M Sc , 199 601–616, 1940

[8] Perlmutter, Martin and Hermann, H B Apparent two year cure of nephrogenic hypertension A M A Arch Int Med , 91 808–811, 1953

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RESULTS

Of the 39 patients with tumors, 34 had hypernephromas, four had epitheliomas of the renal pelvis and one had an encapsulated neurofibroma A good early

effect on the hypertension was observed in 12 of these patients (31 per cent) After a year, however, only 5 patients (13 per cent) had normal blood pressure, four of these 5 patients had hypernephromas and one had an epithelioma of the renal pelvis

In this series of 337 patients, 29 underwent sympathectomy in addition to nephrectomy In the opinion of the physician, the urologist and the neurologic surgeon, this combined operation provided the best chance for relief of the hypertension Nineteen of these patients had atrophic pyelonephritis and 10 had other types of unilateral renal disease

The difficulty of evaluating the results of nephrectomy in patients subjected to these combined operations is apparent In fact, such evaluation probably is impossible However, if only a unilateral sympathectomy and nephrectomy are performed and the blood pressure decreases to a normal level, Uihlein[10] has stated that this good effect probably is obtained from excision of the kidney Unilateral sympathectomy was combined with nephrectomy in 10 of these 29 patients Three of these patients had excellent results, two of the three had atrophic pyelonephritis and one had nonatrophic pyelonephritis with calculi Additional patients who were benefited were included in the 19 for whom bilateral two-stage sympathectomy as well as unilateral nephrectomy was done These cases will not be analyzed further because of the difficulty in their evaluation

Excluding from further study the 39 patients with renal tumors and the 29 who had a combination of sympathectomy and nephrectomy, there remain 100 patients with atrophic pyelonephritis and 169 who had miscellaneous surgical renal disease

It might be well to dwell on how the diagnosis of atrophic pyelonephritis is made and how one distinguishes between a kidney that has atrophied because of infection or other causes and the so-called hypoplastic kidney Emmett and associates[11] stated after an exhaustive review that it was impractical and almost impossible to attempt to distinguish these conditions clinically, pathologically or urographically with any degree of accuracy I have, therefore, grouped all the shrunken kidneys in one category

Barker and Walters[2] noted hypertension in 26 (46 per cent) of 57 cases in which a diagnosis of chronic atrophic pyelonephritis was made urographically Baggenstoss and Barker,[12] after an intensive necropsy study of 84 cases of unilateral renal atrophy and 13 cases thought to represent hypoplasia, reviewed the clinical records of the patients concerned and found that 40 per cent had hypertension before their death Both these studies appear to indicate more than a casual association between the two conditions Evidence in support of this theory should result from a comparison of both early and late results of nephrectomy in patients with atrophic kidneys and the results in the group that includes all other unilateral renal disease (tables 1 and 2) These data indicate that better results

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[10] Uihlein, Alfred Personal communication to the author

[11] Emmett, J L, Alvarez-Ierena, J J and McDonald, J R Atrophic pyelonephritis versus congenital renal hypoplasia J A M A 148 1470–1477, 1952

[12] Baggenstoss, A H and Barker N W Unilateral renal atrophy associated with hypertension Arch Path, 32 966–982 1941

TABLE 1 *Early* results after nephrectomy for hypertension associated with severe unilateral renal disease*

Disease	Total patients	Good effect		Poor effect	
		Patients	Per cent	Patients	Per cent
Atrophic pyelonephritis	100	63	63 0	37	37 0
All other renal conditions	169	64	37 8	105	62 2

* One month after operation or at time of surgical dismissal

TABLE 2 *Late* results after nephrectomy for hypertension associated with severe unilateral renal disease*

Disease	Total patients traced	Good effect		Poor effect	
		Patients	Per cent	Patients	Per cent
Atrophic pyelonephritis	64	35	54 6	29	45 4
All other renal conditions	100	25	25 0	75	75 0

* *One year or more after operation*

TABLE 3 *Effect of nephrectomy for hypertension in renal diseases other than atrophic kidney (excluding tumor)*

Disease	Patients	Good early effect	Good effect 1 to 15 years	Poor or no effect
Hydronephrosis with or without stones	80	33	15	47
Chronic pyelonephritis with or without stones including staghorn type	58	24	8	34
Simple cyst single or multiple	10	1	0	9
Tuberculosis	16	4	1	12
Miscellaneous	5	2	1	3
Total	169	64*	25	105†

* Twenty-two were followed less than 1 year
† Forty seven were followed less than 1 year

are obtained after nephrectomy for atrophic pyelonephritis than can be expected after nephrectomy for other types of unilateral renal disease No provision has been made in these tables for fair results, if any doubt occurred, results were classed as poor

This arbitrary division into good or poor effects refers almost entirely to the blood pressure A substantial number of patients whose blood pressure did not decrease to normal levels benefited greatly from the operation Headaches disappeared and general health improved, many stated unequivocally that the nephrectomy undoubtedly was responsible for such improvement They did not take medicine of any kind The blood pressure in some patients remained at a normal level for years but after 10 or 12 years it gradually increased (for example, to 170/110), whereas prior to nephrectomy it may have averaged 230/140 It would be difficult to deny that such a patient had profited from operation, but such patients are listed as having poor effects

Of the patients who had atrophic pyelonephritis, 70 per cent were female, this condition, as observed clinically, apparently predominates in the female sex Benefit obtained from nephrectomy appears to occur about equally in each sex

Whereas 80 per cent of the patients who had atrophic pyelonephritis were 50 years of age or less, only 48 per cent of those with other conditions were 50 or less Further review was made to see whether the results of operation were better in the younger patients in both groups than they were in older patients, significant differences could not be found

Results in the various types of renal disease other than atrophic kidney are summarized in table 3

COMMENT

The early effects of removal of a diseased kidney often are extremely striking Routine preoperative and postoperative measurements of blood pressure, both systolic and diastolic, show a rather dramatic reduction in pressure when it is going to occur This generally takes place within the first 2 or 3 days Sometimes the pressure goes below the value where it finally levels off In those patients who were not benefited by operation, the postoperative blood pressure usually leveled off at a value near the preoperative reading within 24 hours I was unable to find a single case in which benefit was delayed for several months but finally occurred It appears that the reduction in blood pressure will be apparent very early in the postoperative course if a good permanent effect is to be secured from nephrectomy

All the kidneys were subjected to careful pathologic study in the hope of finding some histologic difference that would contrast definitely with the findings in kidneys removed from patients who did not have hypertension Nothing specific could be found In many cases, vascular sclerosis or pronounced thickening of the vessel wall was observed but its extent and severity were by no means indicative of the results that followed operation The presence or absence of infection apparently did not play a determining role, removal of an uninfected hypoplastic kidney with thin arteries sometimes produced excellent results, while excision of an infected atrophic kidney supplied by extremely sclerotic vessels had no effect whatever Likewise, some patients were benefited permanently by removal of an infected kidney containing either multiple calculi or a large staghorn calculus, whereas the majority of those having practically identical lesions experienced no reduction of blood pressure

Renal damage was extensive in all the cases included in this series, with the exception of those in which hypoplasia was present Nephrectomy was indicated in the majority of instances because of the extent of disease, whether or not hypertension was associated However, in the case of small or atrophic kidneys, there were usually no localizing symptoms to call attention to the abnormality

As already indicated, this series represents only about 11 per cent of the total number of patients on whom nephrectomy was performed in the period under consideration The remainder who had nephrectomy did not have hypertension In addition, many patients with surgical renal disease were subjected to conservative procedures, such as pelviolithotomy, plastic operations on the renal pelvis, partial nephrectomy or nephrostomy, some of these patients had associated hypertension The effect of these surgical procedures on the blood pressure has not been investigated recently

One should not be disappointed or discouraged by the aforementioned lack of a method for accurate selection of those patients who would be certain to obtain permanent reduction of blood pressures after nephrectomy The fact remains that reduction or elimination of hypertension has followed nephrectomy in a substantial percentage of patients in whom severe unilateral renal disease is present Unless specific contraindications to operation can be found, it would appear unwise to postpone nephrectomy for fear of not relieving the patient of the distressing symptoms caused by his severe hypertension Removal of a diseased kidney can be accomplished with extremely little risk to the patient Furthermore, as a rule, the disease is so far advanced that no point exists in saving the kidney The patient has much to gain and little to lose

SUMMARY AND CONCLUSIONS

A study has been made of 337 cases in which a combined diagnosis of hypertension and severe unilateral renal disease was made and in which nephrectomy was performed at the Mayo Clinic during a 15-year period

Comparison of the results of nephrectomy for an atrophied kidney contrasted with those following nephrectomy for other severe unilateral renal disease reveals that a much better response insofar as reduction in blood pressure is concerned is observed in the atrophic group

Nephrectomy should be done for the hypertensive patient who has severe disease in one kidney and whose other kidney is normal, provided, of course, that other conditions which prohibit operation are absent

Nephrectomy provides permanent reduction of the blood pressure to normal levels in at least 50 per cent of cases in which an atrophic kidney was present and in about 25 per cent of cases of all other surgical renal disease, with the exception of tumor would be difficult to deny that such a patient had profited from operation, but such patients are listed as having poor effects

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THE POTENTIAL USE OF VIBRATION FOR THE DISINTEGRATION OF CALCULI*

HOWARD I SUBY

From the Massachusetts General Hospital, Boston, Mass

Interest and experimentation for many years in the disintegration of urinary calculi have pointed up the fact that both the physical and chemical nature of the calculus are of great importance Physical and chemical methods for the disintegration of calculi, likewise, have both had their place in calculus therapy We have noted for many years that stones of essentially the same chemical composition have varied in their susceptibility to dissolution Their physical characteristics differed Some stones were hard and some stones were soft, and the amount of interface varied Stones that formed rapidly, however, were usually soft and tended to dissolve rapidly in proper solutions Fragmentation of urinary calculi *in vitro* with its increasing surface production always has increased the speed of dissolution The surface area of a cube can be doubled if the cube is broken into eight cubes, and quadrupled if the cube is broken into 64 cubes The smaller the pieces the more grams of stone per minute can be dissolved

Fragmentation of calculi is far from new Many of our oldest surgical instruments have been designed to accomplish this very phenomenon, and thus in certain selected cases spare the patient from open surgery The various lithotrites, dependent on the personal factor of the operator, have done and are doing a good job

Vibration for the disintegration of stones or hard objects has long been a popular engineering maneuver The jack hammer used in wrecking is a typical example The same principle is used in orthopedic surgery with the cast cutter The efficiency, however, of the cast cutter and jackhammer is based upon 1) the relative vibratory effect and the strength of the tool, and 2) the relative stability of the doomed product The back and forth vibration of the cast cutter head on the hard and immobile plaster cast causes the plaster of Paris to disintegrate, whereas the soft tissue underneath which is not rigidly firm or fixed is relatively unaffected Writing on glass has utilized this same principle The use of this same principle for the disintegration of calculi seemed worthy of consideration, and in 1946 some interest and work in this direction were started

A consideration of vibration naturally entailed at the outset a consideration of frequencies The energizing vibration to be harnessed for experimentation could, depending on frequency, be

1) *Sonic* in the audible range below fifteen thousand cycles per second with a relatively low coefficient of disintegration, but with a relatively small heat problem and with relative safety, or

2) *Ultrasonic* in the inaudible range of fifteen thousand cycles per second (15 Kc) and up Frequencies as high as five hundred million cycles per second have been

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass , June 4-6, 1956

* Engineering and technical assistance from the Raytheon Manufacturing Co

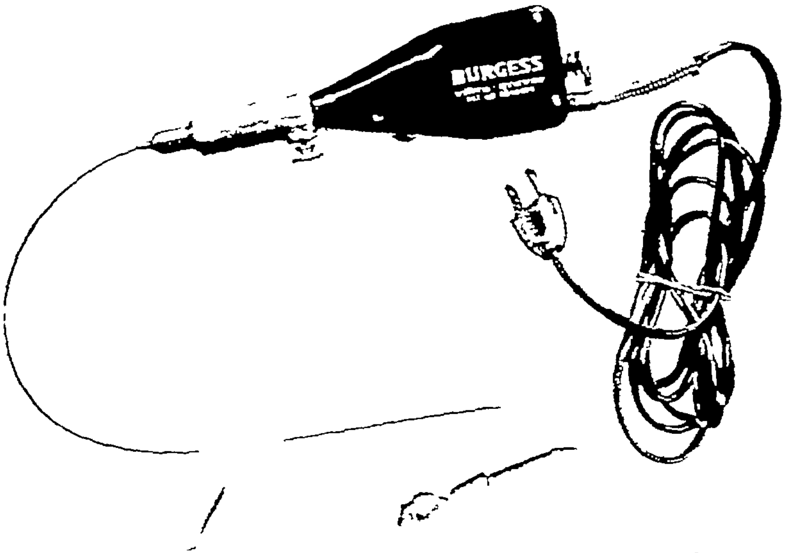

FIG 1 Working element with modified radon seed implanter and tip

developed experimentally (Karlin, B Ultrasonics New York McGraw-Hill & Co 1949) Energizing forces in this range have a relatively high coefficient of disintegration but generate considerable heat which creates a difficult safety problem Ultrasonics have proved their efficiency in industry as in machine tool and die production the coagulation of mine dust and in many other diversified practical fields

Envisioning the usefulness of such a vibrating tool for impacted prostatic or bladder calculi in diverticula or even possibly for impacted ureteral calculi, an instrument was devised in November 1946 utilizing a glass writer The working element was made by the Burgess Vibro-Crafters Incorporated of Grayslake, Illinois, and vibrated in the sonic range of thirty-six hundred strokes per minute The problem of transmitting this force to a remote object was partially answered by utilizing a modified radon seed implanter—a coiled wire sheath with a Monel wire obturator (fig 1) A triangular cone-shaped steel head was used on our original instrument as the cutting tool Holding any type of calculus in one s hand or on a firm surface it became simple to fragment it quickly and completely by exposing the piece, then pieces of stone to the vibrating tool No pain nor evidence of soft tissue damage could be noted on the hand The instrument seemed to have merit it did not cause undue heat, and it performed well *in vitro* With the absence of heat in the sonic range a sheath was not completely necessary The friction between an obturator and the sheath obviously did influence the efficiency of the cutting tool but it did protect the ureter from heat in cases where higher frequencies were used (fig 2)

Following these preliminary experiments attempts were made to disintegrate urinary calculi (calcium oxalate) which had been placed in autopsy specimens

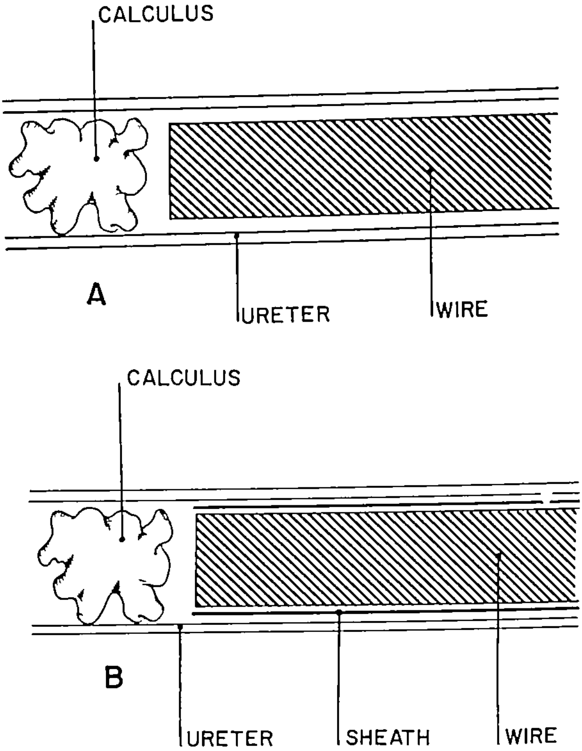

FIG 2 *A*, no sheath in sonic range *B*, sheath for insulation with high frequency

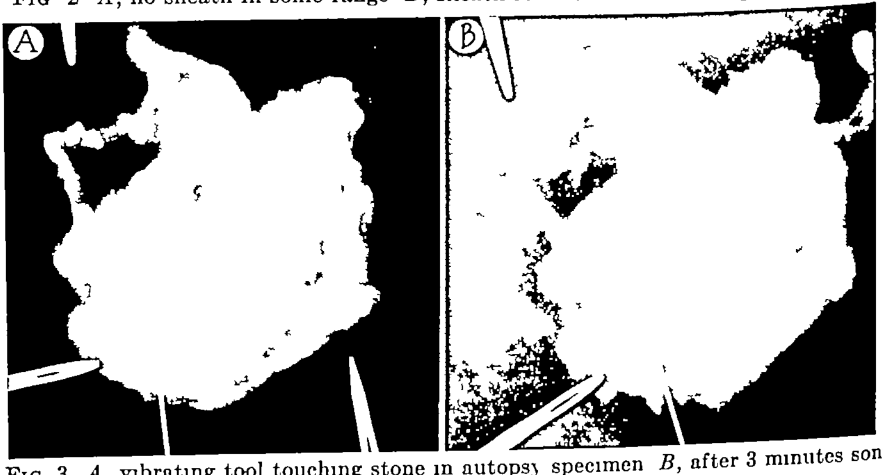

FIG 3 *A*, vibrating tool touching stone in autopsy specimen *B*, after 3 minutes sonic low frequency vibration

Actual urinary stones had been placed in the lower third of the ureter and our vibrating tool was passed up to a point contacting the stones It was at this juncture that part of our shortcomings and potential difficulties became apparent Our vibrator was working well, but the efficiency of the experiment was far below that of the *in vitro* experiments when the stone was held rigidly Flesh is soft and malleable, and the stone with the surrounding ureter were all vibrating together with the working-nose of the instrument with but very little fragmentation taking place If the stone was not slowly pushed up the ureter, or if the instrument did not bypass the stone, some good effect was obtained, but this effect was of poor efficiency Figure 3 is a roentgenogram of an autopsy specimen with the vibrator in contact with a calcium oxalate ureteral stone This stone was completely fragmented by manipulation for three or four minutes

This sonic vibrating instrument was first used on a patient on October 16, 1947

CASE REPORT

W C , M G H No 1816, a 48-year-old man, had an external urethrotomy in 1932 for a urethral stricture Since that time he had had recurrent prostatic and bladder calculi, with calculi in diverticula He was admitted to the Massachusetts General Hospital on October 10, 1947 and on October 15 many of the stones were removed from the bladder Several, however, in diverticula were inaccessible, and it was believed that these might be disintegrated with our new tool On October 16, 1947 these stones (fig 4) were disintegrated by vibration

Subsequent use of this instrument on low ureteral stones seemed to indicate that this frequency tended merely to push the stone back up the ureter, or to vibrate the stone with the surrounding tissues The potential of the instrument still remained very questionable, and in early 1947 the help of Dr Fay of the Massachusetts Institute of Technology was solicited Inquiry into the potential of ultrasonic vibration was made, but most of the experts seemed to think (and it later became verified) that heat could become a really difficult problem In some rather crude experiments I was never thoroughly impressed that the increase in frequency gave enough more fragmentation to justify the heat, but these experiments were never carried out to the point of proof at that time

Further work is now being carried out at the Raytheon Manufacturing Company Whereas the most ideal goal to seek might be the disintegration of calculi

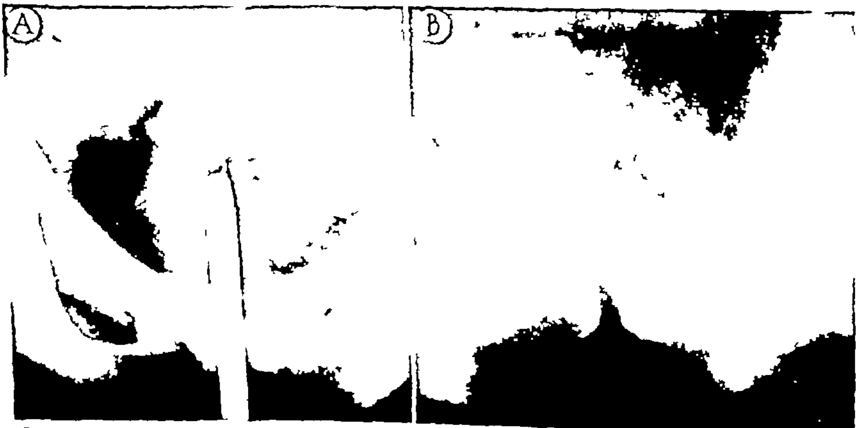

Fig 4 *A* vibrating tool through cystoscope in contact with stone *B*, after disintegration by vibrating tool

by extremely high frequencies transmitted to the stone through the urine or some other liquid introduced into the urinary tract, or directly through the surrounding soft tissues, it has seemed to me that we might probably have more immediate "potential" using lower frequencies until we have learned more about tissue damage. Ultrasonic vibration can be produced by several methods—electrical excitation of barium titanate, quartz crystals, and certain other metals. We have used the method employing an electrically excited nickel stack. Each nickel plate is separated from the next plate by a coat of nickel oxide, and vibration occurs outward from the center to a nodal point. This vibration is transmitted through a tool cone, and a Monel wire on the tool cone acts as the test cutting tool. Selection of the transmitting wire is of considerable importance, as it is imperative to get a substance that is somewhat malleable but that cannot be compressed too much by any form of stress. We have utilized both tungsten and Monel wires, single or multiple, for this purpose. For our basic engineer experiments we have used single Monel wires. Construction of the drill head is also of great importance. We have used square, round, and pointed types, solid and hollow. Lamport and Newman have felt that a hollow type of drill head is

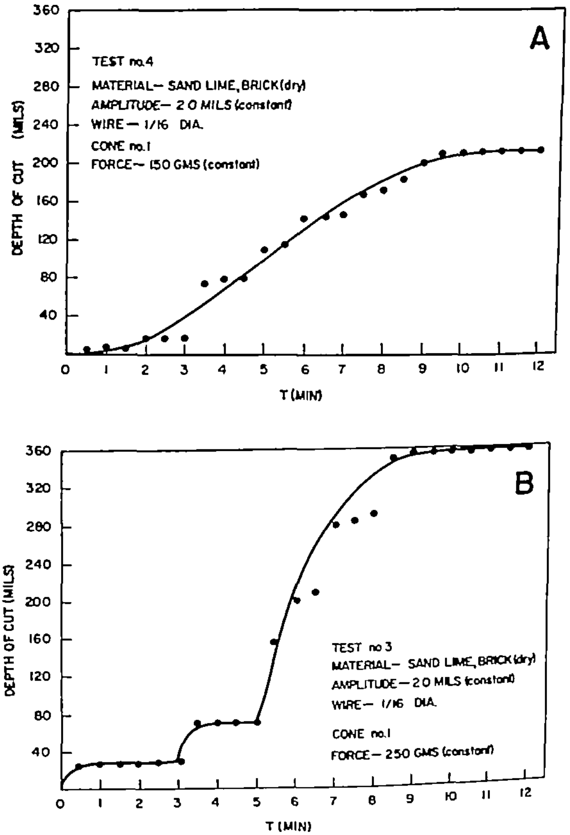

FIG. 5. A, smooth drilling experiment curve. B, irregular drilling experiment curve.

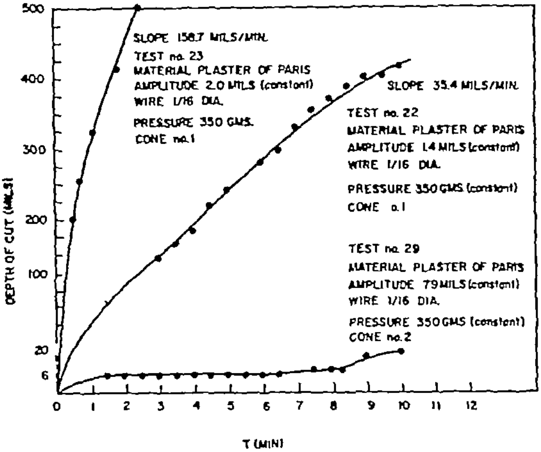

FIG 6 Effect of varying amplitudes at constant frequency (25,000 CPS)

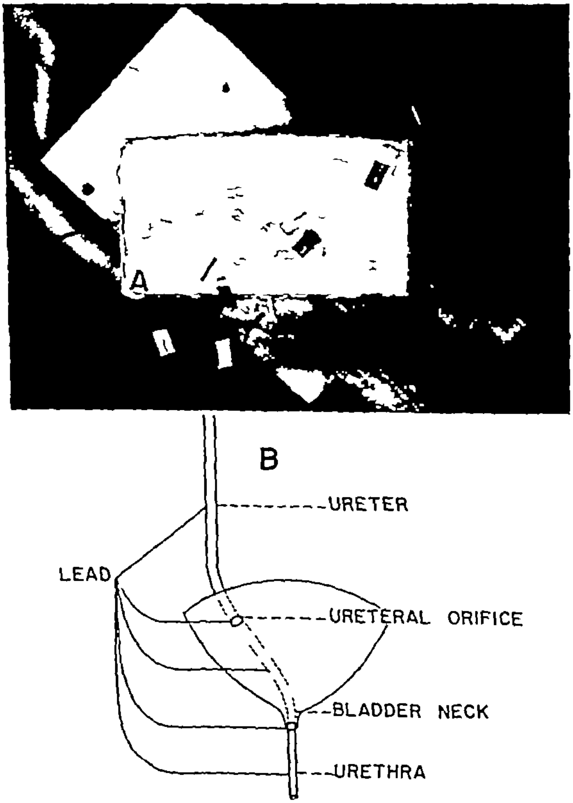

FIG 7 *A* plaster of Paris mold with imbedded angulated sheath *B*, diagrammatic drawing of leads from sheath to thermocouple

much more efficient than a solid drill head, and that it tends to avoid veering off the stone

Attempts have been made to procure a substance whose consistency approximates that of a calculus so that carefully controlled experiments to determine the by extremely high frequencies transmitted to the stone through the urine or some other liquid introduced into the urinary tract, or directly through the surrounding soft tissues, it has seemed to me that we might probably have more immediate "potential" using lower frequencies until we have learned more about tissue damage Ultrasonic vibration can be produced by several methods—electrical excitation of barium titanate, quartz crystals, and certain other metals We have used the method employing an electrically excited nickel stack Each nickel plate is separated from the next plate by a coat of nickel oxide, and vibration occurs outward from the center to a nodal point This vibration is transmitted through a tool cone, and a Monel wire on the tool cone acts as the test cutting tool Selection of the transmitting wire is of considerable importance, as it is imperative to get a substance that is somewhat malleable but that cannot be compressed too much by any form of stress We have utilized both tungsten and Monel wires, single or multiple, for this purpose For our basic engineer experiments we have used single Monel wires Construction of the drill head is also of great importance We have used square, round, and pointed types, solid and hollow Lamport and Newman have felt that a hollow type of drill head is

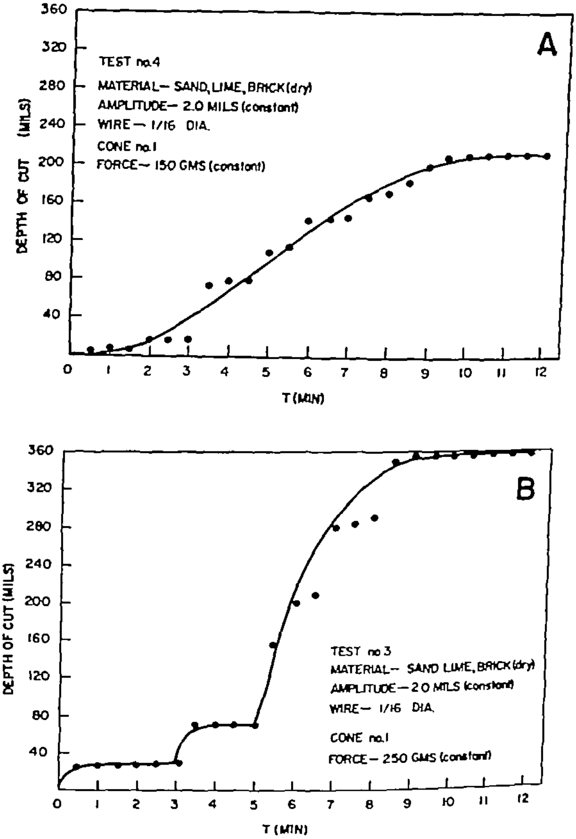

Fig 5 *A*, smooth drilling experiment curve *B*, irregular drilling experiment curve

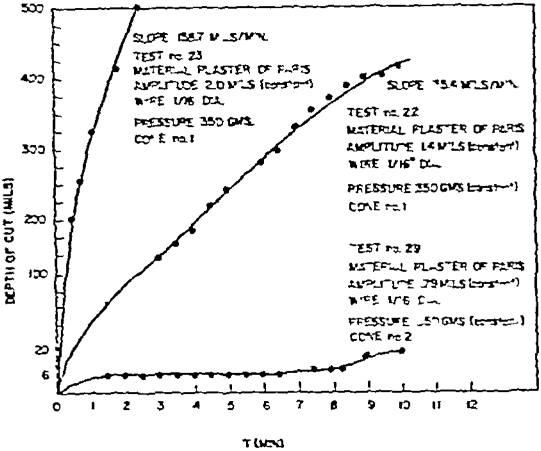

Fig 6 Effect of varying amplitudes at constant frequency (25,000 CPS)

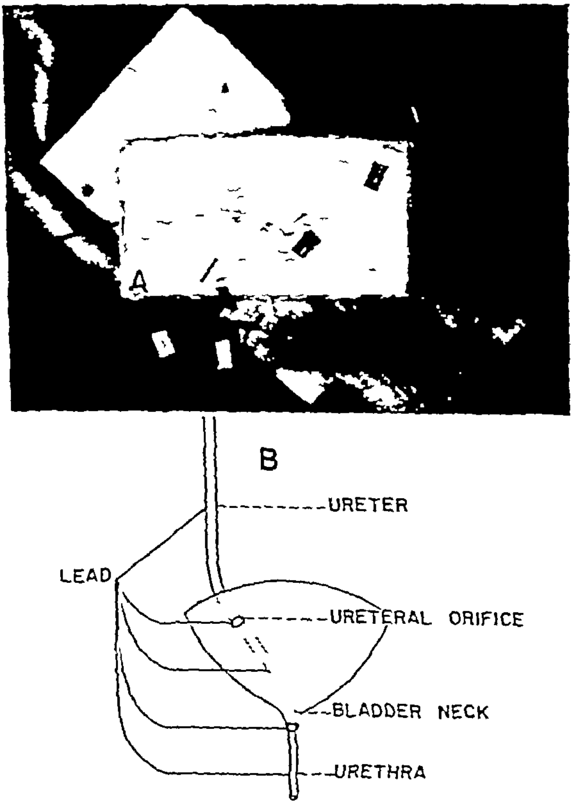

Fig 7 A plaster of Paris mold with imbedded angulated sheath B, diagrammatic drawing of leads from sheath to thermocouple

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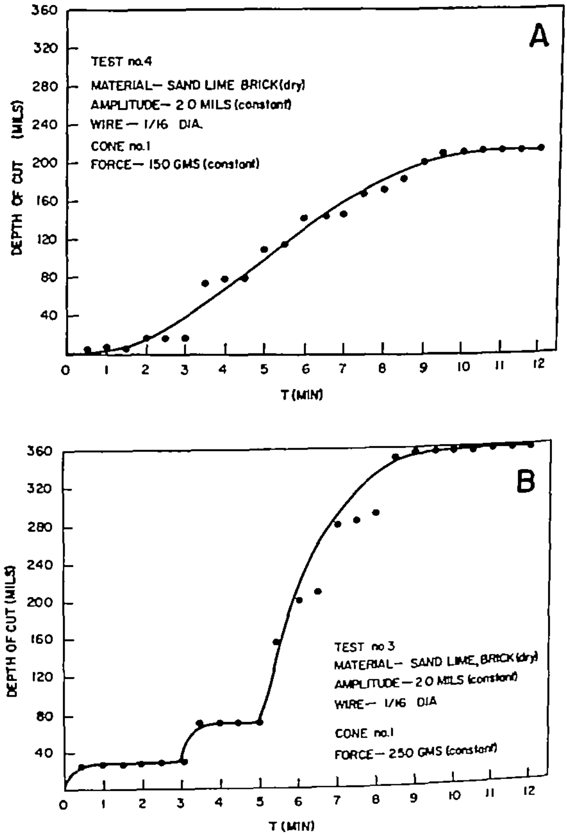

FIG 5 *A*, smooth drilling experiment curve *B*, irregular drilling experiment curve

ureter Obviously the two most acute angles are near the tip of the cystoscope and at or near the ureteral orifice Wires are connected to these strategic points of the sheath where the angulation is most acute and where it is straight and to other parts, and these wires are connected to a thermocouple and potentiometer to measure the exact heat generated at that point by the vibrating obturator Various frequencies and amplitudes can be tried, and different types and sizes of wires, single or multiple, can replace the original wire for comparisons The heat production seems to vary with the first power of the amplitude and with the cube of the frequency Sheaths made from heat-resistent plastics, such as teflon, certain types of nylon, coiled wire, and ordinary woven catheters are being checked The heat problem can be minimized by pulsing, an expression for the periodic off, on, off, on, off, on activation of the working element There should be an optimum pulsing time and pattern for each frequency A modified Johnson stone basket with a hollow sheath and a Monel wire obturator has seemed like a potentially useful instrument for ureteral stones too large to extract easily The stone basket holds the calculus firmly while the obturator connected to a sonic vibrating unit disintegrates the stone Bladder stones too hard to crush or too large to extract with the Lowsley forceps may similarly be disintegrated by vibration using an added obturator The use of water or air-filled cushions (fig 8) as a means of protecting the ureteral wall from the working element is now being tested, and it is felt that if proper mechanical engineering can be effectively directed to accomplish a high degree of safety, this form of therapy may have some potential use There are many problems to be solved before the method will attain clinical importance

SUMMARY

Experiments using sonic and ultrasonic vibration for the disintegration of calculi have been conducted The effect of frequency, amplitude and other engineering variables has been studied Heat production and tissue trauma are the major complicating factors which preclude the clinical use of ultrasonic vibration for calculus disintegration at the present time Calculi in patients have been disintegrated by vibration in the sonic range Vibration may enhance the potential of dissolution therapy Further experimentation is being hopefully but skeptically conducted

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efficiency of different pressures at fixed frequencies, different frequencies at constant pressure, and different amplitudes at fixed frequencies can be done We have used plaster of Paris, but it has not seemed to have the same physical properties as the average urinary stone A form of fire-brick has recently been used This "standard" brick has been divided into small parts and used for experimentation Mr Harvey Miller, Mr George Miller, and Mr Dieter Goetze of the Raytheon Manufacturing Company Research Division have conducted engineering experiments on these substances and on stones As in all experimentation our results have been variable and our curves not constant nor smooth Some drillings may be perfectly smooth, whereas at other times the tool head may drill smoothly for a short time, then stop (presumably at some hard spot in the target) and then resume drilling at a normal rate (fig 5) With single results like this it becomes obvious that each experiment must be done many times before any conclusion can be rightfully drawn Figure 6 is a summary of approximately sixty engineering experiments on plaster of Paris showing the relative efficiency of various amplitudes at a frequency of twenty-five thousand cycles per second It has been very obvious to us that the efficiency of the frequency of forty-three thousand cycles per second is much greater than that of twenty-five thousand cycles per second and because of this it has become possible to drill a stone with very little pressure This frequency is being tested thoroughly at the present time It has become quite evident to me that there should be no great problem in obtaining an optimum working condition so far as drilling or fragmentation of stones is concerned The heat problem, however, is still one of the greatest obstacles to be overcome In a system with a working wire (or wires) inside a sheath the points of greatest heat will be at the points where the greatest angulation occurs We are now trying to find what frequencies and amplitudes, what working wires, and what types of sheath can best help answer this big problem To study this we have constructed a plaster of Paris model imbedded in which is a sheath to be tested, and the working wire or wires (fig 7) This sheath is bent to conform to the exact angulations which a ureteral catheter takes from the mid cystoscope to the mid

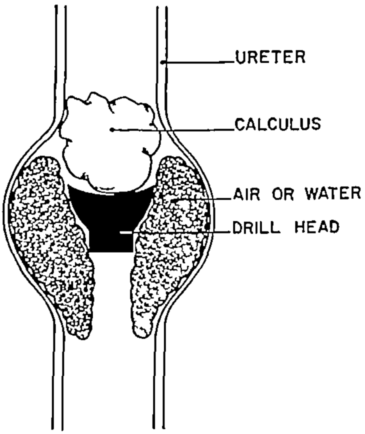

FIG 8 Protective units separating ureter from cutting tool

ureter Obviously the two most acute angles are near the tip of the cystoscope and at or near the ureteral orifice Wires are connected to these strategic points of the sheath where the angulation is most acute and where it is straight and to other parts, and these wires are connected to a thermocouple and potentiometer to measure the exact heat generated at that point by the vibrating obturator Various frequencies and amplitudes can be tried, and different types and sizes of wires, single or multiple, can replace the original wire for comparisons The heat production seems to vary with the first power of the amplitude and with the cube of the frequency Sheaths made from heat-resistent plastics, such as teflon, certain types of nylon, coiled wire, and ordinary woven catheters are being checked The heat problem can be minimized by pulsing, an expression for the periodic off, on, off, on, off, on activation of the working element There should be an optimum pulsing time and pattern for each frequency A modified Johnson stone basket with a hollow sheath and a Monel wire obturator has seemed like a potentially useful instrument for ureteral stones too large to extract easily The stone basket holds the calculus firmly while the obturator connected to a sonic vibrating unit disintegrates the stone Bladder stones too hard to crush or too large to extract with the Lowsley forceps may similarly be disintegrated by vibration using an added obturator The use of water or air-filled cushions (fig 8) as a means of protecting the ureteral wall from the working element is now being tested, and it is felt that if proper mechanical engineering can be effectively directed to accomplish a high degree of safety, this form of therapy may have some potential use There are many problems to be solved before the method will attain clinical importance

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UNFAVORABLE RESULTS OF ACETYLSALICYLIC ACID IN THE TREATMENT OF RECURRENT UROLITHIASIS

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The purpose of this paper is to report the discouraging results following the use of acetylsalicylic acid in three patients who had a long history of recurrent calcium-containing calculi The stimulus for this type of treatment followed the publications by Prien and Walker[1, 2] who treated a series of nineteen such patients with acetylsalicylic acid Their patients were observed over a twelve to eighteen-month period During this time no growth or new formation of calculi occurred in seventeen This amazingly good result by Prien takes on a special significance with the realization that the methods in use today to prevent recurrent calcium-containing calculi are in general unsuccessful The detailed biochemical basis and the practical reasons for choosing salicylates in the treatment of recurrent calcium-containing calculi have been fully described[1, 2] and will not be repeated in this publication

The three patients whose cases are now being reported had a long history of passing numerous calculi over a period of many years Complete urological studies were done on these patients at one time because of a previous history of calculous disease No evidence of any obstructive uropathy could be demonstrated on these examinations Complete repeated laboratory studies failed to reveal any evidence of hyperparathyroidism The urine was infected in cases 1 and 3 and free of infection in case 2 All had evidence of renal calculi in situ prior to the start of the acetylsalicylic acid therapy In all three patients treated with this drug the existing calculi actually increased in size and density after four months of therapy It may be of some significance to report that no attempt was ever made to measure the total calcium or glucuronoside excreted in the urine, as Prien recommended

CASE REPORTS

Case 1 J M , a 48-year-old man, presented himself with a history of passing four to five calculi each year since 1943 The patient was seen first in April 1951 with a history of right renal colic An excretory urogram at that time revealed three small calculi measuring approximately 2 by 3 mm in their greatest diameter in the lower calyx of the right kidney Another calculus measuring 3 by 4 mm was present in the middle calyx of the left kidney There was no evidence of any hydronephrosis or hydroureter The pH of the urine was 5 5 and free of any infection He was discharged from the hospital pain free and carefully instructed to avoid those foods high in calcium The importance of forcing fluids

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[1] Prien, E L and Walker, B S Studies in urolithiasis IV Urinary glucuronosides and calcium phosphate J Urol , 74 440–446 1955

[2] Prien, E L and Walker, B S Salicylamide and acetylsalicylic acid in recurrent urolithiasis J A M A , 160 355–360, 1956

was stressed He drank ten to twelve glasses of water each day and an additional two glasses of water at bedtime Six months later he spontaneously passed another calculus This was analyzed and reported to consist of a mixture of calcium oxalate and calcium phosphate In spite of passing three to four calculi each year he remained comfortable until May 1954 when he was admitted into the hospital for a right pneumonectomy The right lung had become atrophic because of repeated pleural effusions The etiology of the effusions was never established Prior to this operation an excretory urogram was done A large calculus in the lower calyx of the right kidney measuring 3 by 6 mm in its greatest diameter was noted A smaller calculus was also noted in the middle calyx of the left kidney Urine culture demonstrated Aerobacter aerogenes Although he has been treated with various antibiotics his urine since this time has never remained free of infection In August 1954 he passed a calculus from the left kidney which was proven by roentgenograms On May 28, 1955 he was started on acetylsalicylic acid in the recommended dosage of two grams divided into three equal doses per day Figure 1, *A* is a plain urogram taken 4 weeks prior to the starting of acetylsalicylic acid Figure 1 *B* was taken September 21 1955, approximately 4 months following the aforementioned therapy A striking increase in the size and density of the right renal calculus is apparent

Case 2 D D , a 19-year-old boy, gave a history of having his first attack of renal colic in 1944 Examination at that time disclosed an obstructing calculus in the right mid-ureter This was surgically removed Following the operation the patient was under no medical care in spite of the fact that he passed many calculi during the following 10 years In April 1954 urine examination by the

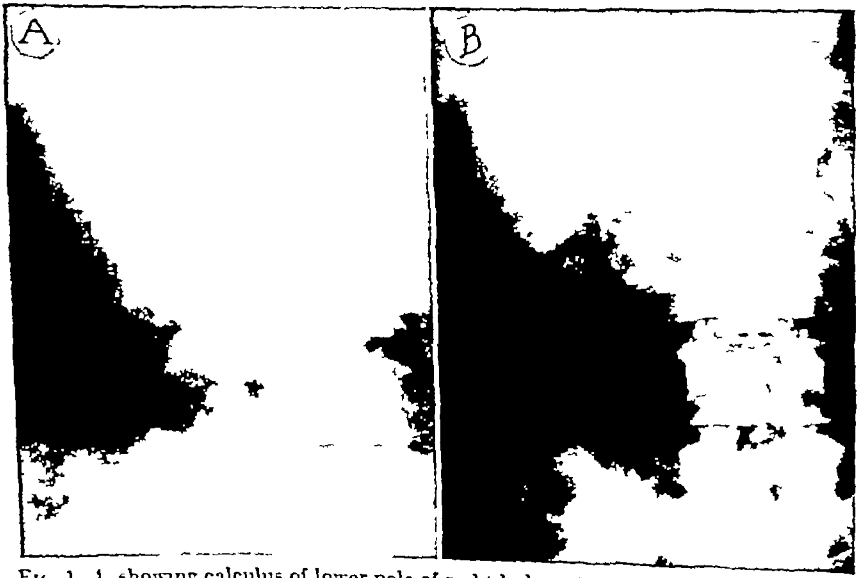

FIG 1 A showing calculus of lower pole of right kidney 4 weeks prior to start of acetylsalicylic acid therapy *B* striking increase in size of right renal calculus is apparent

United States Army showed numerous red blood cells per high power field Because of this finding he was referred to me by his family doctor Urological examination revealed a large calculus in the pelvis of the right kidney measuring approximately 10 by 12 mm in its greatest diameter This was removed surgically without any difficulty The calculus was sent to Dr E L Prien for crystallographic analysis and was found to be composed of calcium oxalate and calcium phosphate The nucleus of the calculus was calcium oxalate Laboratory studies repeated twice failed to reveal any evidence of hyperparathyroidism Six weeks following the operation urinalysis was negative for red blood cells, white blood cells or bacteria After an absence of 9 months the patient reported to me again that he had passed five calculi without any associated symptoms since his last visit Urine examination at this time revealed many red blood cells per high power field without any evidence of infection Figure 2, *A* is a plain urogram taken July 12, 1955 On this day acetylsalicylic acid therapy was started in the usual dosage The importance of drinking water and avoiding dairy products was again stressed This regimen was continued for 14 weeks when another film was taken (fig 2, *B*) A definite enlargement of the calculus is noted on the right side The calculus on the left appears to have increased in size and density

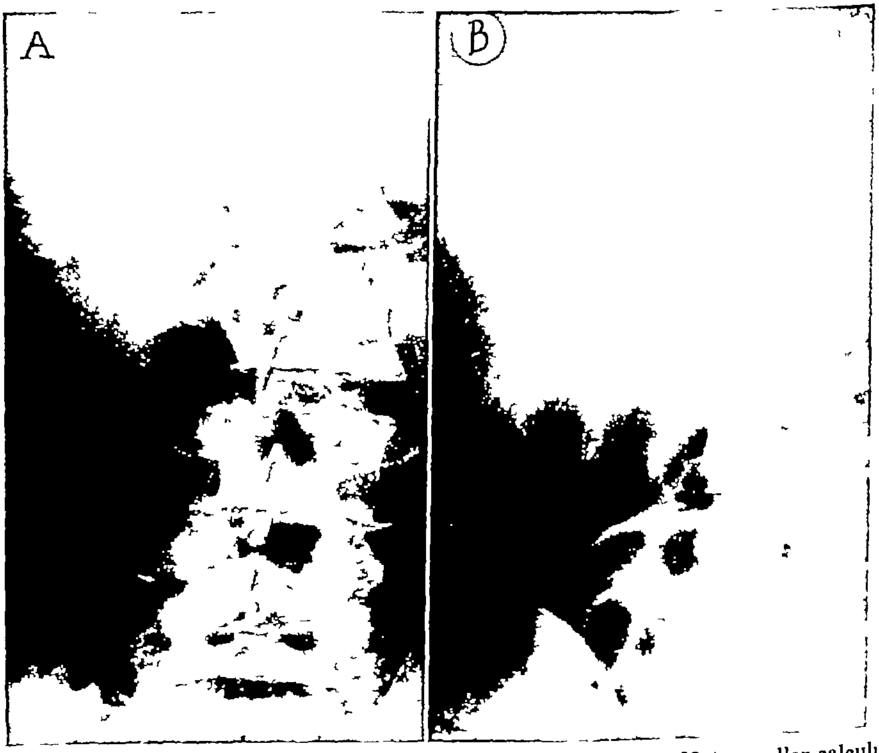

FIG 2 *A*, showing large calculus in region of right renal pelvis Note smaller calculus overlying left kidney Acetylsalicylic acid therapy commenced on this day *B*, fourteen weeks after acetylsalicylic acid therapy Note increase in size and density of both right and left calculus

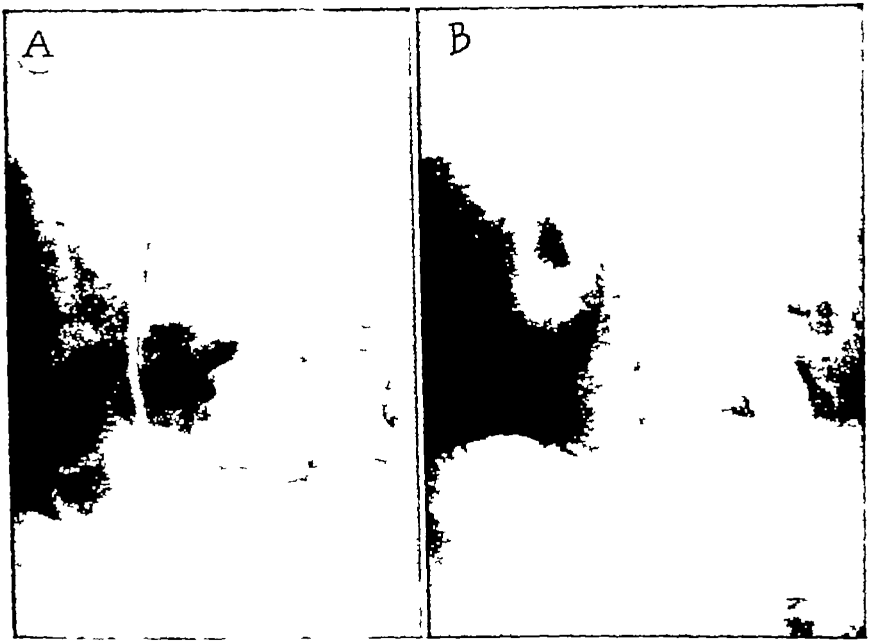

FIG 3 *A*, film taken April 1955 three months prior to start of acetylsalicylic acid therapy *B* showing increase in size and density of calculi

I have no reason to believe that the patient did not follow his diet and faithfully take his medicine

Case 3 D H, a 39-year-old woman was first seen in August 1953 complaining of severe right flank pain She had had similar attacks in the past and passed a total of six calculi during the previous 5 years Urological examination at this time revealed three small calculi in the inferior calyx of the right kidney The largest calculus measured 3 mm in its greatest diameter There was no evidence of any obstructive uropathy Urine culture from the right kidney grew Aerobacter aerogenes which was sensitive to chloromycetin Laboratory studies showed no evidence of hyperparathyroidism She remained symptom-free until January 1954 when she again had right flank pain Soon afterward a calculus was passed The hospital laboratory reported that the calculus consisted of a mixture of calcium oxalate and calcium phosphate Urological examination now demonstrated six small calculi in the lower calyx of the right kidney Surgery was recommended and refused by the patient In April 1955 the patient experienced more right flank pain and examination revealed findings similar to what was noted in January 1954 Figure 3, *A* depicts a film taken in April 1955 On July 25 1955 acetylsalicylic acid therapy was started No new film was taken with the start of this treatment There were no untoward symptoms from this medication until November 1 1955 when the patient again experienced severe right flank pain A film taken at this time (fig 3, *B*) shows an increase in the size and number of calculi in the lower calyx of the right kidney

The significance of these three case reports is to point out that acetylsalicylic acid under certain conditions may actually stimulate calculi to grow In these patients no quantitative calcium or glucuronoside determinations were done, as suggested by Prien The failure to respond to acetylsalicylic acid may have been due to an inability to produce adequate amounts of glucuronosides Since two of the three patients had infected urine it is also possible that excessive destruction of the glucuronosides developed as a result of bacterial action

SUMMARY

Three case histories are presented of patients who had a long history of recurrent calcium-containing calculi and who for this received acetylsalicylic acid (2 gm) daily In all three the existing calculi had grown in size In case 3, new calculi appeared Unfavorable results following the use of acetylsalicylic acid are presented

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REMOVAL OF URETHRAL CALCULI BY JOHNSON STONE BASKET

RAYMOND J. FITZPATRICK

While urethral calculi are commonly encountered, the number of such stones becoming impacted in, or obstructing the urethra is indeed quite small. Kahle and Mellinger[1] reported only 38 cases seen at Charity Hospital in the years 1937 through 1948. The total hospital admissions during that period were 565,027, an admission incidence of 1 in 14,869.

Urethral calculi are of two types: 1) primary—those formed in the urethra and 2) secondary—those which are formed in the kidney, ureter, bladder or prostate and migrate to the urethra. Secondary calculi, according to Herbut, are eleven times as frequent as primary calculi.[2] Most of the urethral calculi causing obstruction occur in patients between the ages of 45 and 55 years, the age period in which prostatic hypertrophy begins to occur, which, in turn, acts as a barrier to the passage of stones. Thus they are much more common in males than in females. In the latter, they are ordinarily associated with diverticula of the urethra. Higgins,[3] quoting English, stated that in a review of 361 cases of urethral calculi, 41.2 per cent were in the posterior urethra, 18.8 per cent were in the bulb, 28.4 per cent were in the scrotal or penile urethra and 11.3 per cent were in the fossa navicularis.

SYMPTOMS AND DIAGNOSIS

The clinical manifestations of obstructing urethral calculi are sufficiently familiar to all urologists to make such repetition at this point merely redundant. The correct diagnosis is established by any one, or combination, of the following: 1) eliciting a careful history, 2) palpating the stone along the ventral surface of the urethra, 3) roentgenography, 4) urethroscopy, and 5) inserting a metal sound to detect that familiar sensation of metal grating on or striking stone. Unless the caliber of the stone is already known from previous studies a plain film of the abdomen, including the genital area, should be made for this purpose, keeping in mind that over 50 per cent of stones of vesical origin are not discerned on the roentgenogram.

TREATMENT

The methods usually suggested for the removal of obstructing urethral calculi are: 1) pushing the calculus back into the bladder and removal by litholapaxy or by other endoscopic means, 2) occluding the urethra proximal to the stone and distending by irrigation the urethra distal to the point of occlusion,[4] 3) when possible, simple extraction with a hemostatic forceps, 4) milking the stone down-

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Accepted for publication October 1[illegible], 195[illegible].

[1] Kahle, P. J. and Mellinger, G. T.: Urethral calculi. Urol. & Cutan. Rev., 53: 674-677, 1949.

[2] Herbut, P. A.: Urological Pathology. Philadelphia: Lea & Febiger, 1952, vol. 1, pp. 12[illegible]-1[illegible].

[3] Campbell, M.: Urology. Philadelphia & London: W. B. Saunders Co., 195[illegible], vol. 1, sec. [illegible], pp. [illegible]-[illegible]57.

[4] [illegible], M. J.: Removal of calculi from urethra. J. Urol., 60: 6[illegible]0, 19[illegible].

ward and out the urethra, 5) urethrolithotomy and 6) suprapubic cystolithotomy Some of the above methods may require for success internal urethrotomy or external urethral meatotomy The author would like to suggest an additional method for removal of calculi with diameters under 2 cm

PROCEDURE

After suspecting or confirming the presence of an urethral calculus, the urethra should be anesthetized to permit instrumental manipulation A 2 per cent tripellenamine (pyribenzamine) solution has been found after five years usage to be a most safe and effective topical anesthetic agent for this purpose[5] [6] Trilene inhalation may be employed along with it for analgesic potentiation if needed Urethral calibration is then performed down to the calculus, but not beyond it for fear of pushing it back into the bladder After localizing the calculus, determining its size, and establishing adequate urethral caliber distal to the stone, a decision is then made as to the best method of removal If the size of the offending calculus is such as to suggest the feasibility of transurethral extraction then a well-lubricated 33 cm standard, woven urethral filiform (No 56 thread) is manipulated past the stone much as one would do preparatory to dilating an urethral stricture A Johnson stone basket is then threaded into the distal end of the filiform and manipulation carried out much as one would do for an ureteral calculus A 33 cm filiform is recommended because, as Nation points out, once it is introduced beyond the calculus it may be withdrawn from the meatus " as many times as necessary without the danger of again being unable to pass beyond the calculus because the long filiform guide is not pulled below the obstructing stone "[7] Engagement of the stone will be facilitated and, at times, made possible only by extraurethral stone fixation This is done either by a finger in the rectum for the purpose of elevating stones out of natural depressions or pockets in the prostatic urethra, or, by grasping the stone between thumb and index finger in the more accessible portions of the urethra, as simultaneous manipulation with the basket is carried out with the opposite hand The procedure may be performed in the office with relatively little discomfort to the patient

It was not possible to find in any of several texts consulted any statement that would suggest the size-limitations of stones that might be withdrawn from the intact urethra We may draw some inferences, however, from our knowledge of, and greater familiarity with, the more frequently encountered problem of ureteral calculi The lumbar spindle of the ureter has an average diameter of 10 mm , the pelvic spindle 6 mm , and, the intramural ureter 3 5 mm A generally accepted rule of thumb states that ureteral calculi larger than 1 cm in diameter rarely pass spontaneously, and that stones more than 2 cm in diameter should be removed by open surgery Theoretically, the diameter of the urethra at any one point, considering the urethra as a perfectly circular tube, would be one-third of its French scale calibration at that point expressed in millimeters In transurethral prostatectomy, calibration to 30F is usually regarded as standard procedure prior to the introduction of the 28F sheath A circular tube therefore calibrated to 30F has a diameter of 10 0 mm or 1 0 cm If the circle were compressed to the point of forming a mere slit, then the new diameter would be equal to approximately one and one-half times the diameter of the circle While the natural elasticity of the urethra would permit some stretching beyond these cold mathematical diameters, nevertheless it would seem wise to restrict extraction of urethral calculi through the intact urethra to those under 2 cm in diameter In other words, the caliber of the stone being extracted should be compatible with the caliber of the urethra it traverses

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[5] Fitzpatrick, R J , Orr, L M and Stubbart, F J Antihistamines as local anesthetic agents for urethral manipulation J A M A , **150** 1092–1094, 1952

[6] Fitzpatrick, R J and Orr, L M Tripellenamine hydrochloride for topical urethral anesthesia J A M A , **158** 261, 1955

[7] Nation, E F Facilitation of passage and extraction of ureteral calculi J Urol 70 373–375, 1953

CASE REPORTS

Case 1 W R , a 32-year-old white telephone repairman, sustained multiple injuries in August 1953 when a telephone pole to which he was strapped toppled over From the genitourinary standpoint, partial disruption of the membranous urethra secondary to severe pelvic fractures with marked ecchymosis and perineal swelling were found Cystolithotomy was performed on December 3, 1953 for vesical calculi that developed after prolonged immobilization and urethral catheter drainage despite daily irrigations with Suby's solution, 500 t r u of hyaluronidase daily from the date of admission, frequent change of catheters and other stone preventative measures Two months after being discharged from the hospital the patient noted a sudden shutting-off of the urinary stream followed by burning and by frequent voidings in very small amounts At times, knife-like pain radiating out to the end of the penis was observed A plain film of the abdomen, including the prostatic area, revealed a calculus measuring 0 8 by 0 6 cm in the prostatic urethra In an effort to find some means of removing this stone without readmission to the hospital and without inserting a rigid instrument into an urethra which resided in a badly scarred perineum, the idea suggested itself of removing the stone with a Johnson stone basket After anesthetizing the urethra with 2 per cent pyribenzamine, the urethral caliber was determined with filiforms and Phillips' followers Upon demonstration of adequate caliber the followers were removed and the stone basket attached to the woven urethral filiform Two or three thrusts were made with the basket but each time as the basket itself emerged from the meatus the stone was not within it A finger was then inserted into the rectum and upward pressure was made on the prostatic urethra containing the stone, to elevate the stone out of any declivity existing in the prostatic urethra With this pressure maintained, the very next thrust of the basket resulted in the successful engagement and extraction of the offending calculus In all, the procedure was accomplished in a few minutes with practically no discomfort to the patient A good stream with no bleeding immediately followed

Case 2 F Del , a 72-year-old white man, was seen in February of 1954 comward and out the urethra, 5) urethrolithotomy and 6) suprapubic cystolithotomy Some of the above methods may require for success internal urethrotomy or external urethral meatotomy The author would like to suggest an additional method for removal of calculi with diameters under 2 cm

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[5] Fitzpatrick, R J , Orr, L M and Stubbart, F J Antihistamines as local anesthetic agents for urethral manipulation J A M A , **150** 1092–1094, 1952

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Since the preparation of this paper, five of several calculi, none of which was obstructing the urethra, were readily removed by stone basket from the prostatic urethra of a patient who was awaiting admission to the hospital for urologic surgery The stones were found on routine urethral calibration, were confirmed by x-ray, and were removed by the basket technique prior to the insertion of a Foley catheter simply to check further on the effectiveness of the method The largest of the stones was 1 2 cm in diameter

An additional and simple method for the removal of impacted or obstructing urethral calculi under 2 cm in diameter is proposed Illustrative cases are presented

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plaining of sudden stoppage of the urinary stream with marked urgency and strangury A transurethral resection of a contracted vesical neck had been performed on December 31, 1953 After urethral anesthetization with 2 per cent pyribenzamine, calibration with a 24F sound revealed a sensation of scratching against the sound in the region of the penoscrotal junction External palpation at this point revealed a stone to be present in the urethra X-ray was not necessary as the calculus could be palpated It was felt that this calculus had probably been sitting in one of the multiple large bladder cellules at the time of surgery and thus not discovered either endoscopically or by previous x-ray A woven urethral filiform was manipulated past the stone and the Johnson stone basket attached to it Because of apprehension, trilene was also administered Backward and forward thrusts with the basket were then made unsuccessfully Since the stone seemed to be of fair size, the question arose as to whether the basket capacity was adequate for it Therefore, the capacity of the basket was increased by outward bending of the wires This maneuver, together with grasping the portion of the urethra containing the stone, permitted immediate successful stone engagement and extraction on the next thrust The stone measured 1 5 by 1 3 cm in diameter A normal urinary stream immediately followed

Case 3 L A T , a 65-year-old white man, was seen on April 20, 1956 complaining of severe knife-like pain radiating out to the end of the penis on attempted voiding His stream, which had been perfectly normal on first arising that morning, suddenly shut off on attempted voiding after breakfast Thence, to the time he was seen some two or three hours later, urgency, strangury, and the passage of a few drops of bloody urine every five to ten minutes was his plight A few weeks previously a plain film of the abdomen had been made elsewhere for right renal colic An ureteral calculus in the mid-third of the right ureter and left nephrolithiasis were found Numerous stones had been spontaneously passed over the previous twenty years, but with none of the previous attacks had the patient ever been plagued with inability to void A plain film of the abdomen on April 20, 1956 revealed a 1 2 by 0 8 cm stone in the region of the prostatic urethra Since no radiopaque calculus was visualized along the course of the right ureter, it was presumed that the ureteral calculus had left the ureter and was now residing in the posterior urethra Under topical pyribenzamine anesthesia, aided by trilene analgesia, the urethra was calibrated down to the stone and was normal A woven urethral filiform was then manipulated past the stone and the Johnson stone basket attached to it A finger was inserted into the rectum and while the stone could not definitely be palpated a feeling of crepitus could be appreciated as the filiform by-passed the stone The basket was inserted into the prostatic urethra and upon its first withdrawal the stone was trapped within it A normal urinary stream followed

SUMMARY

Three cases are presented in which calculi impacted in the urethra were readily and simply extracted at the office by means of a Johnson stone basket attached to a 33 cm woven urethral filiform (No 56 thread) A finger should be inserted

into the rectum for stones in the prostatic urethra or the stone should be grasped between thumb and index fingers when located in the more accessible portions of the urethra, as simultaneous basket manipulation with the opposite hand is accomplished The procedure may be performed under topical anesthesia with or without trilene analgesia The size of the stone and the existence of an urethral caliber estimated to be adequate for its passage should be known before attempting to ensnare and extract it Calibration should extend down to the stone but not beyond it for fear of possibly pushing the calculus back into the bladder For calculi greater than 1 0 cm in diameter, it is suggested that the capacity of the basket cage be increased by outward bending of its wires Whether meatotomy, urethrotomy or endoscopy is indicated depends upon each individual case

Since the preparation of this paper, five of several calculi, none of which was obstructing the urethra, were readily removed by stone basket from the prostatic urethra of a patient who was awaiting admission to the hospital for urologic surgery The stones were found on routine urethral calibration, were confirmed by x-ray, and were removed by the basket technique prior to the insertion of a Foley catheter simply to check further on the effectiveness of the method The largest of the stones was 1 2 cm in diameter

An additional and simple method for the removal of impacted or obstructing urethral calculi under 2 cm in diameter is proposed Illustrative cases are presented

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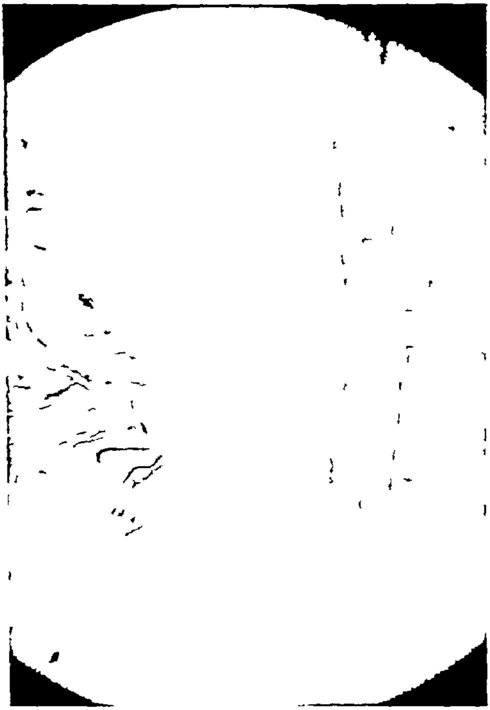
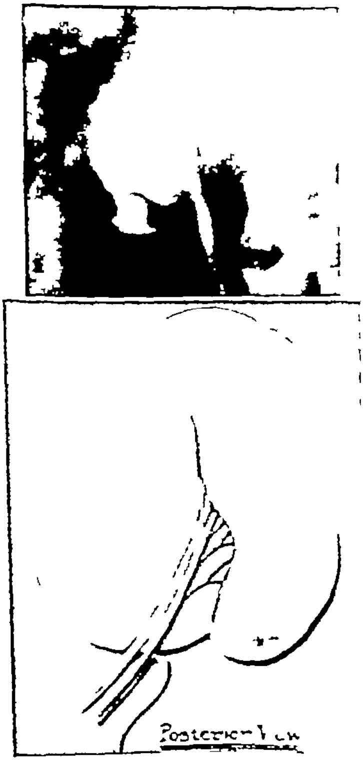


FIG 1 Longitudinal section of normal ureter



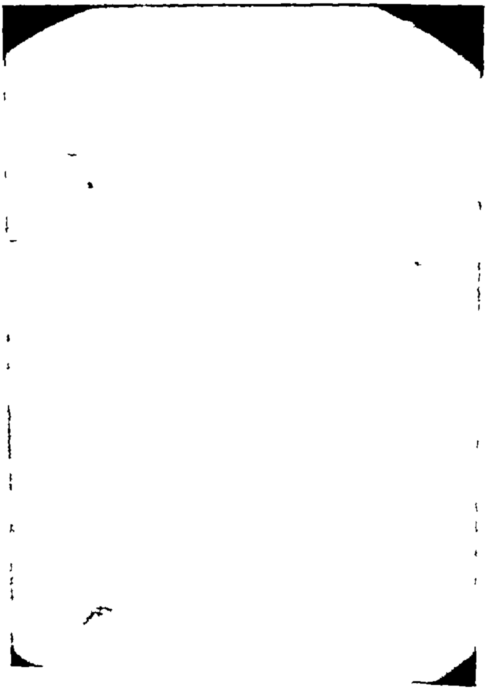


FIG 2 No 13937 A 44 year old married

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A CLINICOPATHOLOGIC STUDY OF URETEROPELVIC OBSTRUCTIONS

ROBERT LICH, JR AND MALCOLM L BARNES

From the Sections of Urology and Pathology, University of Louisville School of Medicine and John N Norton Memorial Infirmary, Louisville, Ky

Interest in ureteropelvic obstruction was stimulated in 1937 when it was noted that interruption of an aberrant renal vessel, that seemingly was obstructing the ureter, was not necessarily followed by a recession of the associated pyelectasis Furthermore, a normal lumen of the ureteropelvic area as determined by antegrade calibration at operation was not always indicative of functional patency any more than cystoscopic retrograde ureteral dilatation would afford anatomical or clinical improvement In fact our experience, like that reported in the literature, made it obvious that the then practiced operative cure of pyelectasis was not always predictable It was assumed that there were factors in operation which were not evident Hence, this study was launched which has extended over many years because of unavoidable interruptions, investigation of false leads and the necessarily limited clinical and pathological material To obtain material for this study it was necessary to excise the ureteropelvic junction in each instance and this necessitated ureteropelvic anastomosis which has been routinely practiced throughout this period of years with gratifying results The evolved method of anastomosis has been described and represents a procedure whose assets embody simplicity and predictable success

Initially it was noted that some specimens revealed a thickened muscular wall with concomitant narrowing of the ureteropelvic junction Muscular or epithelial hyperplasia, increased elastic tissue and a preponderance of collagen were all findings seen on occasion in reviewing the surgical specimens of the ureteropelvic segment

Owing to the inconsistency of these histologic findings longitudinal sections were substituted for the previously studied cross sections Cutting accurate longitudinal sections of the ureteropelvic junction affords certain technical difficulties, but even so it was readily seen that for the first time the mystery of ureteropelvic junction obstruction was beginning to unfold There were found rather frequently finger-like retrograde valvular formations which varied in number and degree It was of interest to observe that these valvular structures appeared equally as often in instances in which there were obstructing aberrant vessels or fibrous bands as when these structures were not in evidence Furthermore, there existed a direct relationship between the degree of valvular formation and the associated pyelectasis The presence of these valve-like structures explained why antegrade calibration of the ureteropelvic junction was often meaningless as a method of determining the functional capacity of this lumen This study has shown rather distinctly that pyelectasis due to ureteropelvic obstructions is most often associated with intrinsic ureteral changes and that extrinsic factors seldom play more than a minor secondary role

Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass , June 4–6, 1956

FIG 1 Longitudinal section of normal ureter

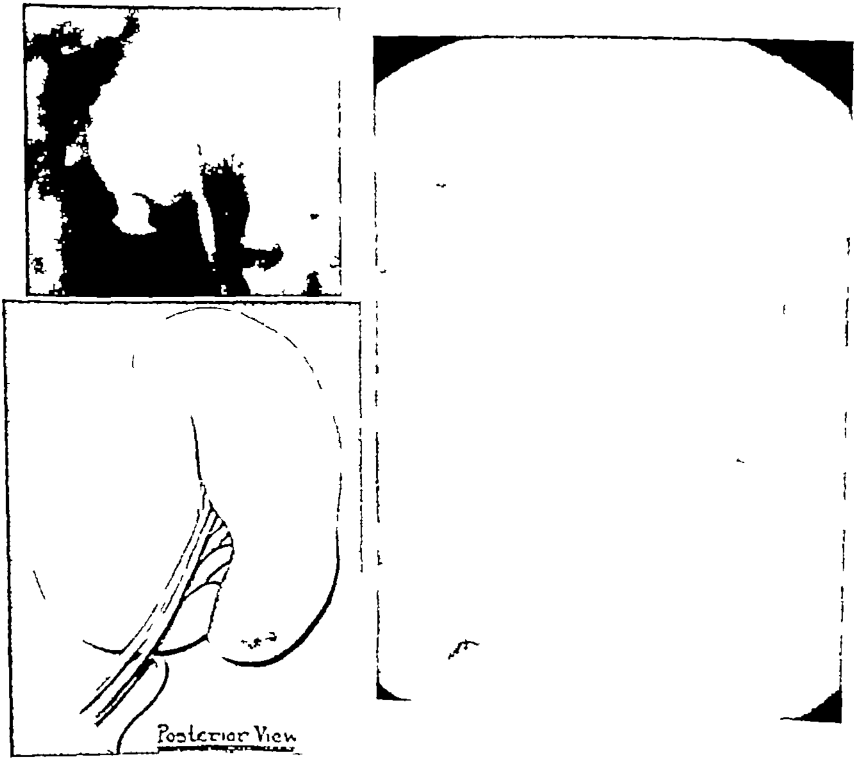

FIG 2 No 13937 A 44 year old married woman with 10 year history of recurrent pyelonephritis Vessels are of no obstructive importance

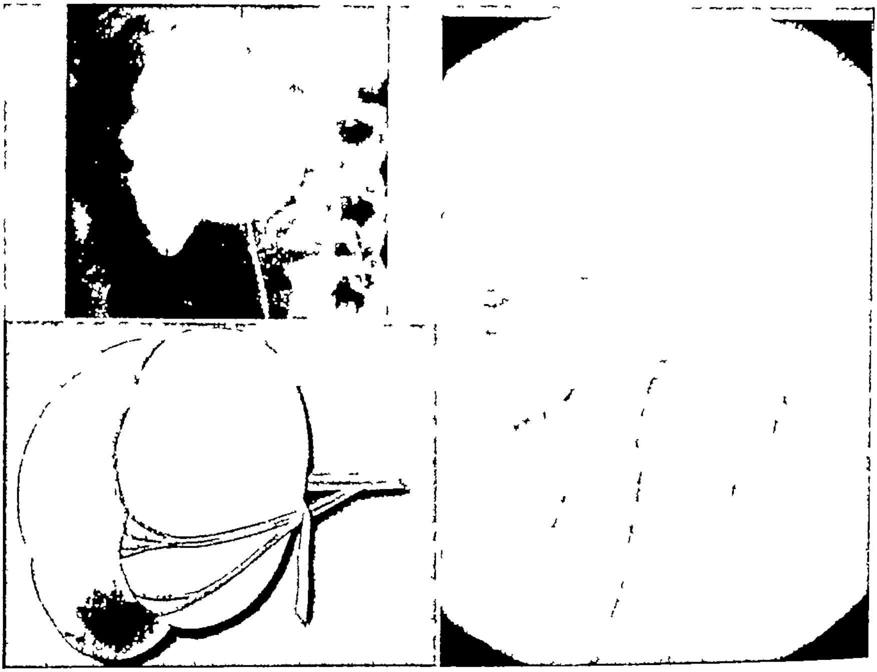

FIG 3 No 140012 A 20 year old girl with a functionless right hydronephrosis Obstructive vessel at ureteropelvic junction is prominent

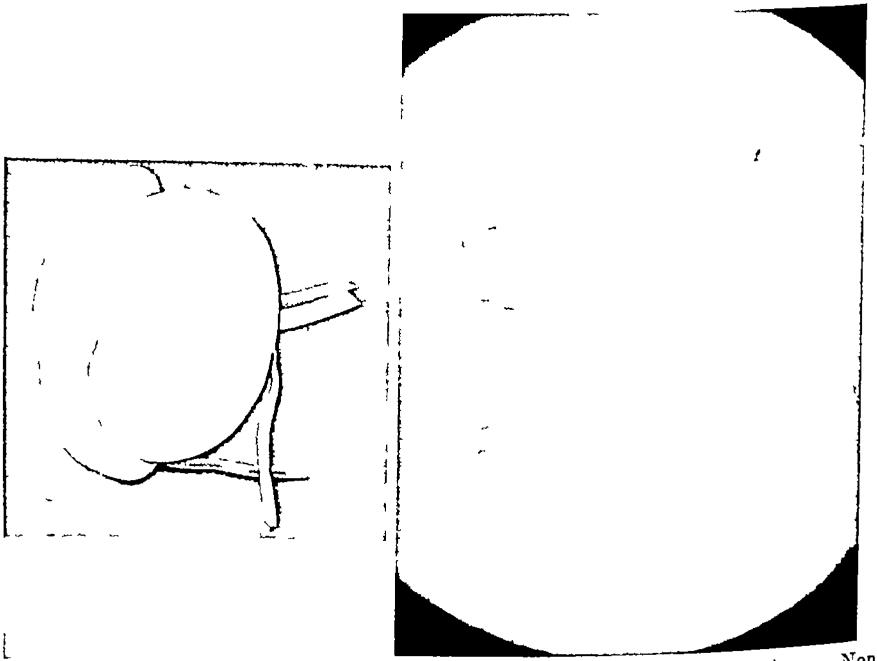

FIG 4 No 157488 A 57 year old man with a noninfected right hydronephrosis Nonobstructive aberrant vessel crosses the ureter

In figure 1 the normal microscopic appearance of the ureteropelvic junction is demonstrated The epithelium is relatively smooth with the ureteral wall of uniform thickness and without cellular infiltration or submucosal edema To obtain good photomicrographs of the normal ureteropelvic area was difficult since the longitudinally cut sections would float apart on the slide so that both walls of the specimen could not be seen in the same field of the microscope

In figure 2 the pyelogram demonstrates the degree of hydronephrosis The drawing of the operative findings shows little if any evidence of ureteral obstruction by the abnormal course of the renal pedicle It is true that the pedicle seems to indent the pyelectatic renal pelvis, but ureteral compression was not evident at the time of pyeloplasty The photomicrograph of the ureteropelvic junction demonstrates the large valve-like structure (the tip of which was broken in slide preparation) pointing (upwards) toward the renal pelvis On the opposite side near the top of the photomicrograph there can be seen the base of another valve In the midportion of this photograph is seen a valvular structure which too was

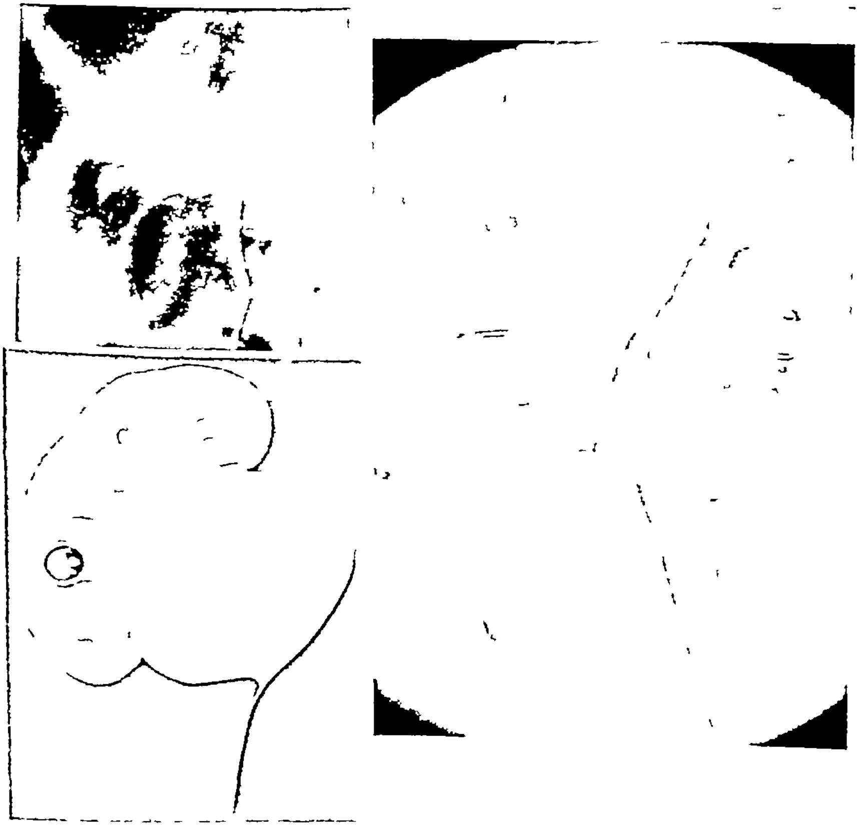

Fig 5 No 371333 A 47 year old housewife with pyuria and nephrolithiasis No aberrant vessels or band

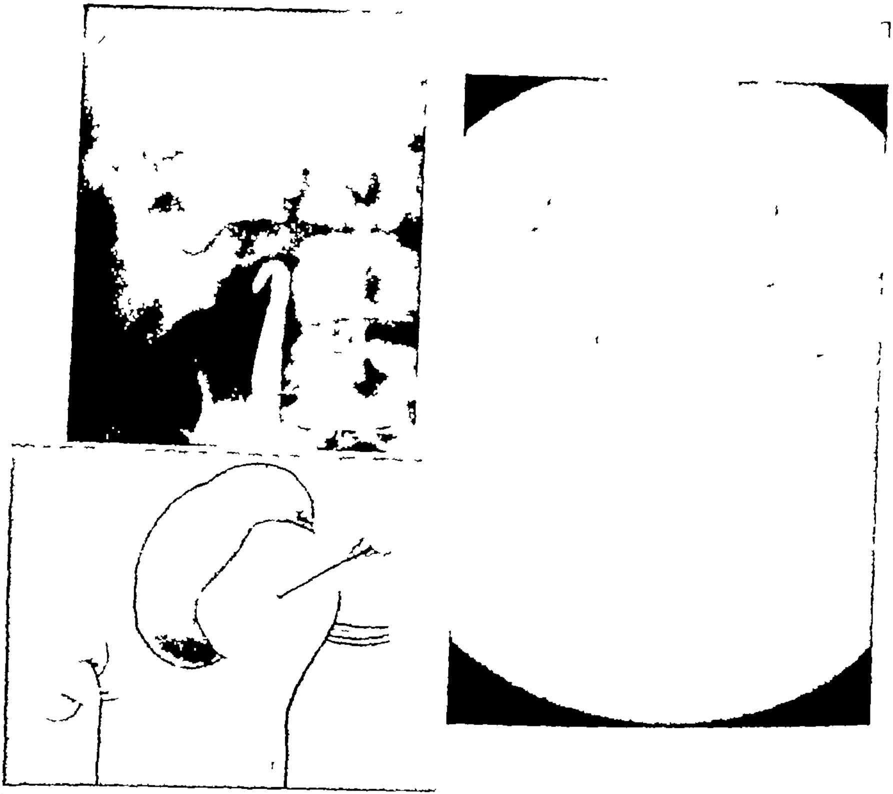

Fig 6 No 152572 A 27-year-old housewife with right pyelonephritis and hydronephrosis Intermittent ureteropelvic obstruction unrelated to aberrant vessels or bands and nephroptosis

quite obstructive as the several slides were reviewed The rather marked inflammatory infiltration is due to this patient's prolonged recurrent renal infection

Figure 3 demonstrates a marked functionless hydronephrosis in a 20-year-old girl In this instance the aberrant vessel seemingly obstructed the ureter The photomicrograph demonstrates striking ureteropelvic valves which most graphically bear witness to the factor of intrinsic obstruction Here again there is marked submucosal cellular infiltration and edema since pyelonephritis was the prominent symptom

Figure 4 presents the findings in a 57-year-old man who suffered with "lumbago" for years The pyelogram was virtually identical with that of figure 3 At surgery a high insertion of the ureter was found and the aberrant vessel was of no obstructive importance The photomicrograph shows a multiplicity of ureteral valves projecting toward the renal pelvis with minimal inflammatory reaction and only moderate submucosal edema

Figure 5 demonstrates the findings in a patient with back pain and a calyceal stone The ureteropelvic obstruction found on urography occasioned the resection of the ureteropelvic junction at the time of pyelolithotomy The accompanying photomicrograph of the ureteropelvic junction demonstrates a singular small valvular structure which was rather distinct in reviewing the many sections through this area, but here we have epithelial hyperplasia as the primary cause of obstruction

Figure 6 presents the findings in a most interesting patient A 27-year-old housewife was admitted because of repeated episodes of undiagnosed fever and pain in the right flank The urine from the right kidney was heavily infected A ureteropelvic obstruction was evident in the urogram, but the cause of the moderate hydroureter was unexplained and incidentally disappeared postoperatively At surgery, when the kidney was exposed, it was somewhat disconcerting to find a normal kidney with no evidence of pyelectasis, as shown in the small insert However, when the renal pelvis was injected with saline there appeared a most prominent ureteropelvic obstruction and marked pyelectasis which would not drain into the ureter even with manual compression of the pelvis The multiple valve-like formations in the accompanying photomicrograph are evident

SUMMARY

The subject of intrinsic ureteropelvic obstructions is discussed The common finding of retrograde valve-like formations is presented and their appearance is unrelated to secondary extrinsic factors of ureteral compression

801 Heyburn Bldg, Louisville 2, Ky

REFERENCE

Lich, R, Jr, Maurer, J E and Barnes, M L Pyelectasis J Urol, 75 12–16, 1956

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THE RESULTS OF Y PLASTY AFTER FIVE TO TWENTY FOUR YEARS A REVIEW OF SEVENTY THREE OPERATIONS

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While intermittent hydronephrosis from obstruction at the ureteropelvic junction is said by Troup to have been recognized as early as 1672, over two hundred years elapsed before Trendelenburg first tried to correct it surgically in 1886 Causative lesions may be congenital or acquired included are strictures, accessory vessels to the lower pole, fascial sheets and bands (fig 1), postinflammatory fibrosis external to the junction, valves as well as granulomas and polyps of the mucosa, high attachment of the ureter to the pelvis, nephroptosis (fig 2), and neuromuscular dysfunction Combinations of two or more of these are common It may be that accessory vessels and ptosis are more often contributory than exciting causes, and it is uncertain whether high ureteral attachment is a cause or an effect of hydronephrosis (fig 3) The exact nature of "neuromuscular dysfunction" is unsettled, spasm of the junction, hypotonia of the pelvis, and dysinnervation of both have been suggested as causes, but the term really means only that the ureter is normal and the pelvis dilated in the absence of demonstrable anatomical obstruction

The disorder is usually discovered during urography done because of renal pain, or of persistent or recurrent urinary infection The essential feature is a dilated pelvis with a normal ureter, the nature of the underlying lesion may or may not be detectable

If pain is unmistakably renal, or if the hydronephrosis is infected, one concludes that surgical treatment is needed If, however, the symptoms are atypical or the hydronephrosis is small, particularly in the absence of infection, additional diagnostic measures are needed Distension of the renal pelvis through an ureteral catheter may prove the relationship between hydronephrosis and pain by reproducing the latter, but only if the patient is unaware of the purpose of the maneuver, otherwise suggestion may cause confusion However, if the pain produced by distension differs in character and in location from that of the original complaint, it is safe to assume that the origin of the symptoms is extrarenal

The delayed retrograde pyelogram is also valuable If one fills the pelvis with contrast agent, removes the catheter, and has the patient walk about for ten minutes, radiography should show an empty or virtually empty pelvis Delay in evacuation, particularly if the calyces are clubbed, strongly suggests genuine obstruction

As Nesbit recently emphasized, a patient may have genuine renal pain, yet have a normal urogram between attacks, whereas one made during pain, either spontaneous or induced by diuresis, may disclose frank hydronephrosis

Differential diagnosis may be difficult in a patient who complains of digestive disturbances and who proves to have hydronephrosis only after studies of the

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass, June 4–6, 1956

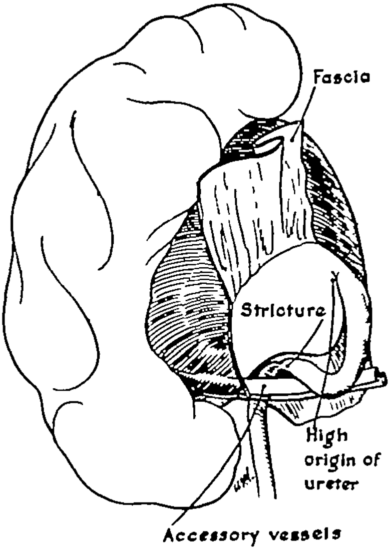


FIG 1 Composite diagram of accessory vessels, stricture and fascial sheet in obstruction at ureteropelvic junction

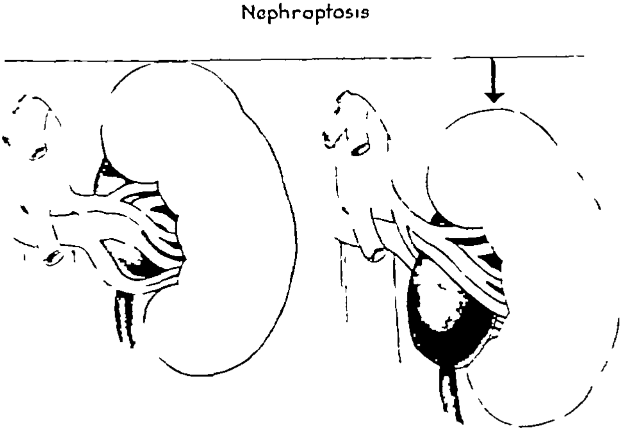


FIG 2 Probable role of nephroptosis in ureteropelvic obstruction

gastrointestinal tract have been normal It is tempting to advise operation in these circumstances, but one must remember that the renal lesion may have nothing to do with the complaints Hellstrom Giertz, and Lindblom, O'Conor, and Gibson have concluded that certain hydronephroses may reach equilibrium and thereafter fail to progress or cause trouble This situation may be recognized by the absence or atypical character of the symptoms, and from the fact that urograms made at fairly long intervals show no increase in the dilatation One should be particularly skeptical of any causative relationship between digestive disturbances and small hydronephroses, while large ones may undoubtedly disturb gastrointestinal function by pressing upon adjacent organs

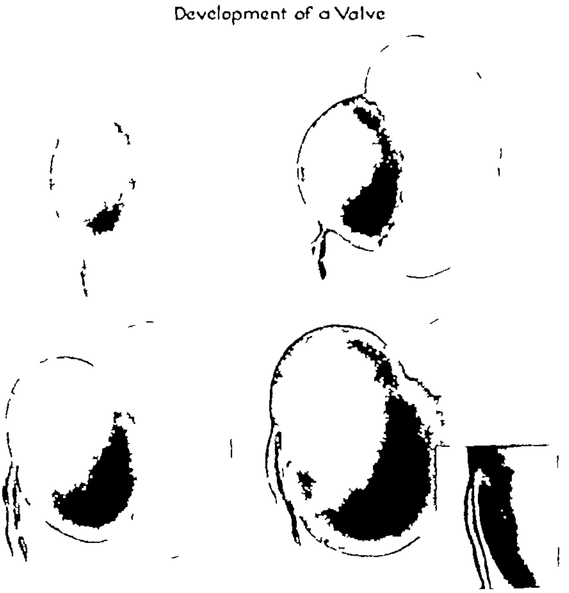
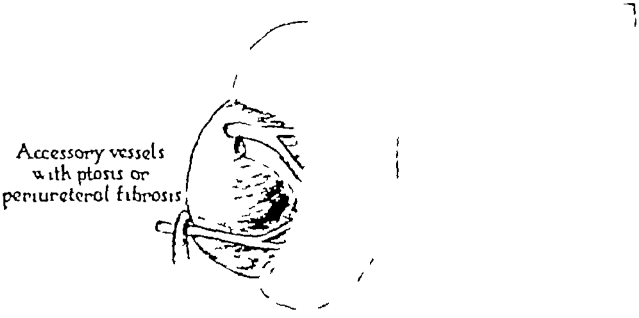


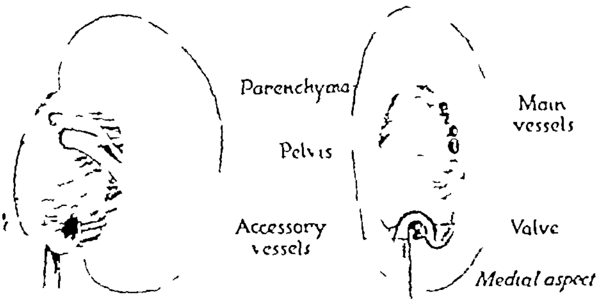
FIG 3 Development of acquired high origin or attachment of ureter

Having ascertained that a noncalculous obstruction is causing symptoms severe enough to require surgical treatment, one must decide whether the kidney should be repaired or removed Several factors have to be considered First is the functional and anatomic state of the affected kidney It has been proved that half a normal kidney, or even less if there has been opportunity for compensatory hypertrophy, can support comfortable life This can be determined pretty accurately from excretory urography, indigo carmine excretion, and from inspection and palpation at operation If one half of the parenchyma remains and if its color is normal, the kidney is usually worth saving If the kidney is discolored, it may be useful to have a fast frozen section examined to avoid leaving an organ seriously damaged by infection or fibrosis Doss has suggested that aortography be used to determine, from the blood supply, whether an organ is salvageable, but the necessary information can usually be secured without this extra procedure

Another factor is the state of the opposite kidney, the presence in which of any disease, however mild, intensifies the need to preserve its mate A third important consideration is the age of the patient There is but little reason to save the kidney of an individual whose opposite organ has remained normal for 60 years if there is any doubt of the feasibility of doing so On the other hand, the kidney of a child or young person will be exposed to the possibility of disease for so long that conservation of renal tissue is important This attitude is re-enforced by Sargent's observation that removal of a kidney with fair function may so increase the volume of urine excreted by the other side as to convert a latent, unrecognizable noncalculous obstruction into a genuine one requiring treatment When the obstructed kidney is a solitary one, there is no choice



Accessory vessels posterior to ureter (*rare*)



Accessory vessels anterior to ureter (*common*)

FIG 4 Accessory vessels to lower pole of kidney

Before discussing the type of plastic operation best suited to a particular situation, it is desirable to deal with the problem of accessory vessels to the lower pole. While many experienced surgeons agree that they can cause obstruction *per se* (fig 4) and while Quinby suggested that the pounding of an artery against the ureter could interfere with peristalsis, pathologists see at autopsy many such vessels without hydronephrosis, Bell mentions 77 examples of accessory vessels, only 20 of which were associated with hydronephrosis. Moreover, so called neuromuscular dysfunction is fairly common, and I know of no dependable method of identifying it in the presence of polar vessels. It has often been suggested that this can be determined if, after separating them from the junction, one observes the rate at which saline injected into the pelvis flows down the ureter. Unfortunately, I am never sure whether the rate is normal.

I have therefore preferred to perform a plastic upon the junction if there is any doubt whatever that the vessels cause the hydronephrosis, thus avoiding the risk of missing a functional obstruction. I realize that arguments can be presented upon the other side.

While it is generally agreed that an artery which supplies more than one fifth of the kidney should not be cut, and that veins of considerably larger size may be sacrificed, one's attitude will vary with circumstances. If the opposite kidney is abnormal or absent one will want to do the least possible damage. If the other one is normal one may compromise a little more parenchyma with a clear conscience If too much tissue becomes cyanotic with temporary occlusion of the vessels, one should consider some variant of Patch's method of dividing the renal pelvis and suturing it in front of them Since this does not obviate overlooking a co existing functional obstruction, it seems wiser to divide the junction itself and to make a terminolateral anastomosis between ureter and pelvis in the manner of Wilhelm, Nesbit, and others (fig 5) Young excised diamond shaped pieces from the anterior and posterior surfaces of the pelvis and sutured them so as to displace the junction downward away from the vessels I believe that this principle

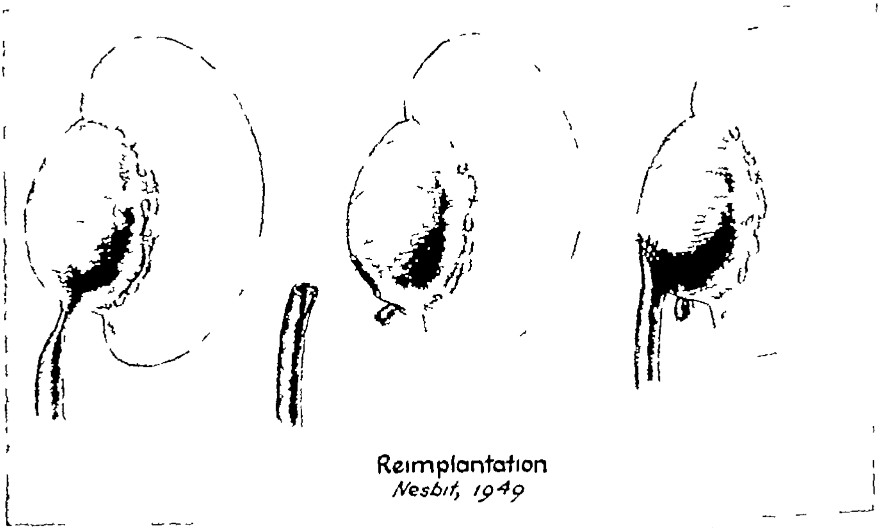


FIG 5 Terminolateral anastomosis (After Nesbit)

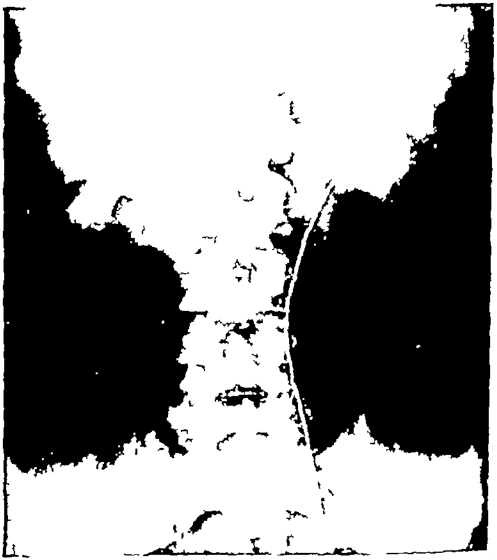


FIG 6 Compression of renal pelvis by vessels left well above ureteropelvic junction at Y plasty

is unsafe I once preserved a pair of sizeable vessels after Y plasty had displaced the junction well below them, because the opposite kidney was functionless A subsequent pyelogram made because of persistent obstruction demonstated that the vessels had indented the dilated pelvis an inch above the ureteropelvic junction, reoperation disclosed that the lumen behind them was filiform, while the junction was normal in caliber (fig 6)

Stewart has altered the relationship between vessels and junction by approximating the poles of the kidney with the aid of capsular flaps sutured together medially with satisfactory results, but this is subject to the disadvantages already mentioned

My own preference in the majority of instances of noncalculous obstruction has been for Foley's modification of Schwyzer's operation (fig 7) It is admirably suited to all types except those with pelves so large as to require partial excision to prevent postoperative pooling of the urine, and those with strictures too long to be widened by any obtainable flap It has two outstanding advantages continuity of pelvis with ureter is maintained so that complete postoperative disruption cannot occur, and the ureteropelvic junction is made dependent

If a stricture is too long to be corrected by the conventional Foley Y plasty, and the pelvis is not large enough to require partial excision, the modification devised by Culp and DeWeerd (and independently by Prince and Scardino and by Gordon) (fig 8, *1*) is useful Very few strictures are too long to be corrected by this method, the advantages of Y plasty are retained

When the pelvis is so large as to require partial excision, a slight modification

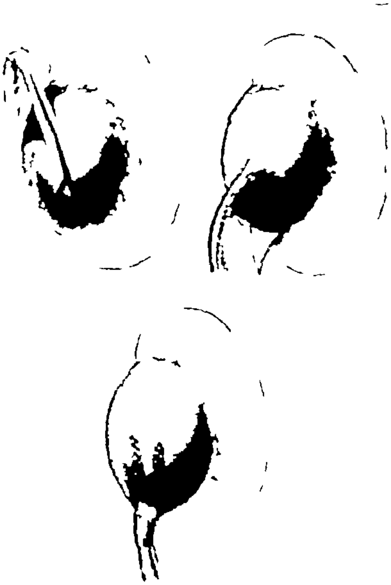


Fig 7 Foley's Y plasty

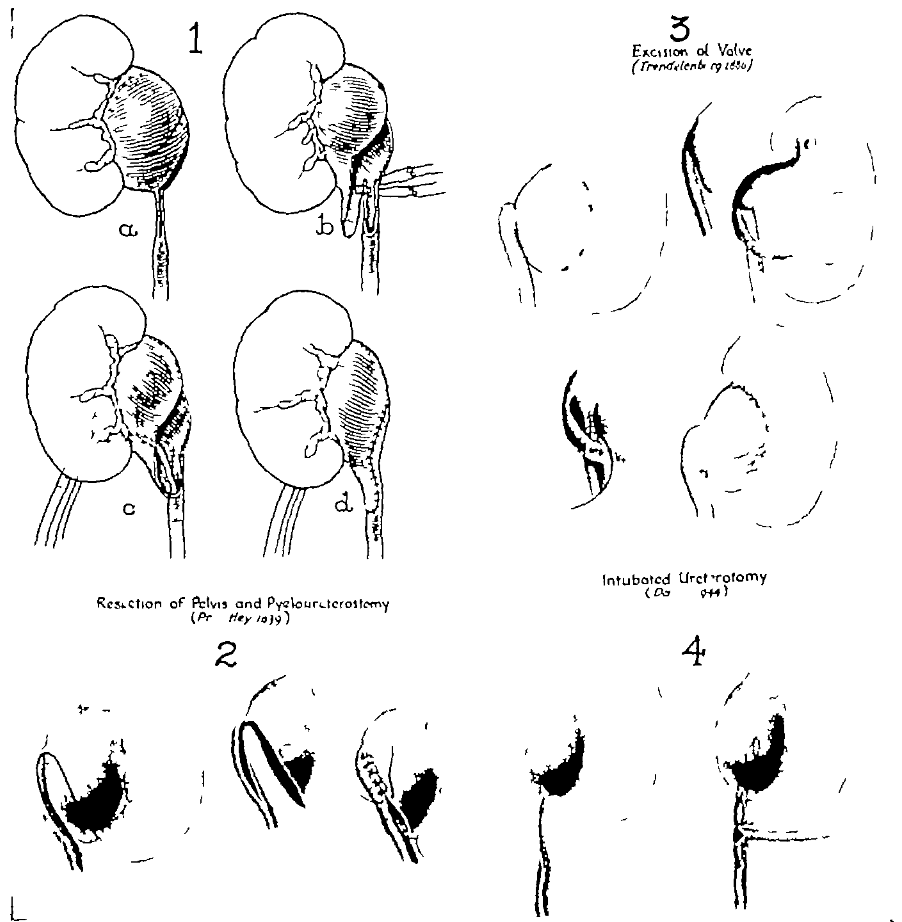


FIG 8 *1*, Method of Culp and DeWeerd *2*, Priestley's operation *3*, Trendelenburg's technique *4*, Intubated ureterotomy of Davis in its early or simple form

of Priestley's operation (fig 8, *2*) may be considered His original method resembles that of Trendelenburg (fig 8, *3*) done from without instead of from within the renal pelvis One can make the excision so as to leave a long flap at the inferior margin of the pelvis, and this can be sutured into a slit in the ureter as in Y plasty The same result can be achieved by partial resection of the pelvis with terminolateral anastomosis of the ureter to it after closure of the resultant defect, but continuity of pelvis and ureter is not maintained

When the stricture is long and the pelvis small (an unusual situation), Davis' intubated ureterotomy (fig 8, *4*) is invaluable My only patient with such a condition had had traumatic avulsion of the ureter from the pelvis of his solitary kidney, late nephrostomy, and an unsuccessful intubated ureterotomy prior to admission, and had worn a nephrostomy for 2 years No flap could be made from the shrunken pelvis In lesions which can be corrected by other means, I prefer to use them because it seems to me that the protracted use of an inlying catheter in the pelvis greatly increases the danger of an intractable infection, particularly with urea splitters Moreover prolonged wearing of such a tube is a great nuisance for the patient

In the rare event of destruction of a segment of the upper ureter so that it cannot reach the pelvis, the operation of Neuwirt should be remembered anastomosis of the ureter to the lower calyx with or without resection of the parenchyma around it Since this is an antiperistaltic arrangement, one wonders whether use of a segment of ileum would not be preferable

Having selected a technique suited to problem of the individual, the next question is that of diverting the urine to protect suture lines during healing Until Hamm and Weinberg published their views, this was just a matter of nephrostomy versus pyelostomy They maintain that catheters serve merely to convey bacteria to the kidney Anyone who has seen lithiasis from urea-splitting bacteria ruin the end result of a meticulously performed plastic will give serious thought to their suggestions

Both nephrostomy and pyelostomy have advantages and disadvantages In the former the renal end of the catheter can be fixed well away from the anastomosis insuring both adequate drainage and freedom from pressure upon suture lines if necessary the catheter can be changed without much difficulty and without disrupting the repair Its chief disadvantage is the fact that renal tissue injured in making it serves as an excellent culture medium thus fostering infection even the miracle drugs may occasionally fail here

Pyelostomy does not have this weakness but it is difficult to place the tube so that it drains efficiently without impinging upon suture lines Replacement is likely to be difficult and removal of the catheter may burst suture lines unless a Robinson catheter is used this is more apt to slip out prematurely than is the Malecot which I prefer The Foley catheter requires a fairly large pelvis to drain effective

There is no general agreement about the necessity or desirability of "splinting" the anastomosis with a catheter or polyethylene tube except in the case of intubated ureterotomy of which it is an essential part From the viewpoint of Hamm and Weinberg it is objectionable and evidence of its virtue except in the situation just noted is lacking Priestley prefers to use a splint and Gibson calls [illegible] except in the "double Fenger" plastic Here the junction is slit [illegible] through both layers and sutured transversely It is not clear why it is [illegible] here but vital in essentially similar operations I suspect that the [illegible] the splint is to prevent suturing across the lumen of the anastomosis [illegible] has been made the catheter may be withdrawn I must admit [illegible] renal disease or upon solitary kidneys I splint the [illegible] T[illegible] also decreases the danger of postoperative [illegible]

CLINICAL MATERIAL

T[illegible] 81 Y plastics [illegible] 5 [illegible] 25 years ago [illegible] Ages ranged from 18 [illegible] to respond to ques-

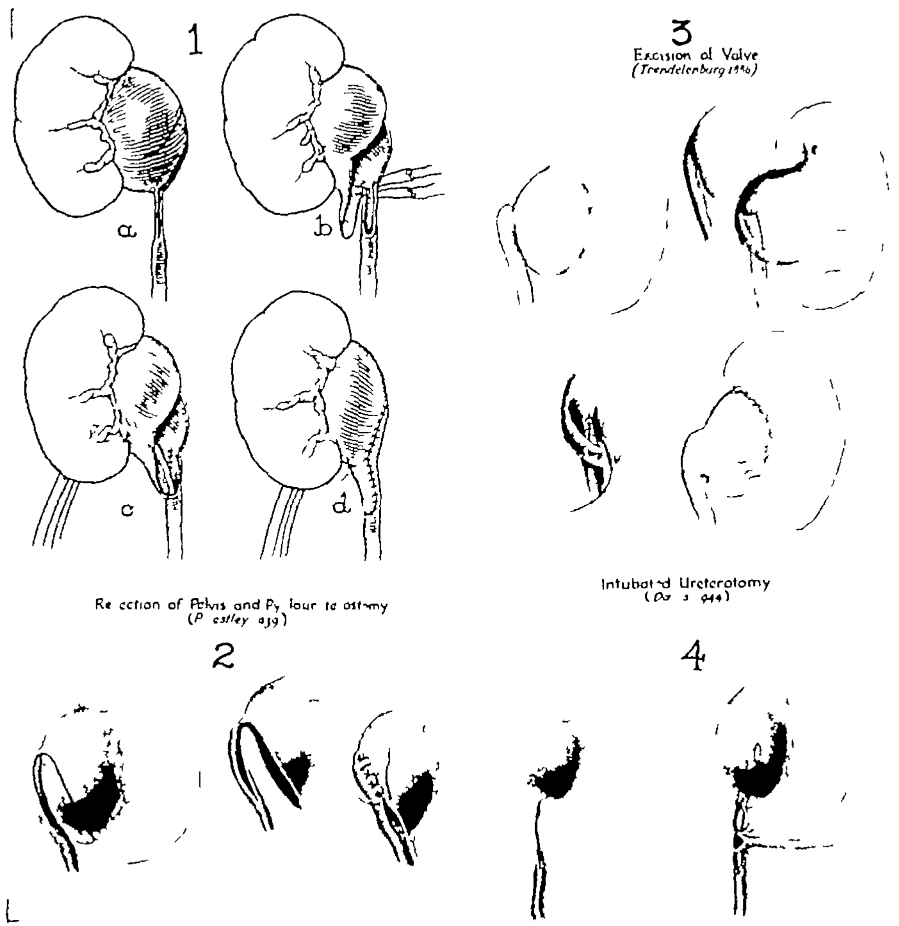


Fig 8 *1,* Method of Culp and DeWeerd *2,* Priestley's operation *3,* Trendelenburg's technique *4,* Intubated ureterotomy of Davis in its early or simple form

of Priestley's operation (fig 8, *2*) may be considered His original method resembles that of Trendelenburg (fig 8, *3*) done from without instead of from within the renal pelvis One can make the excision so as to leave a long flap at the inferior margin of the pelvis, and this can be sutured into a slit in the ureter as in Y plasty The same result can be achieved by partial resection of the pelvis with terminolateral anastomosis of the ureter to it after closure of the resultant defect, but continuity of pelvis and ureter is not maintained

When the stricture is long and the pelvis small (an unusual situation), Davis' intubated ureterotomy (fig 8, *4*) is invaluable My only patient with such a condition had had traumatic avulsion of the ureter from the pelvis of his solitary kidney, late nephrostomy, and an unsuccessful intubated ureterotomy prior to admission, and had worn a nephrostomy for 2 years No flap could be made from the shrunken pelvis In lesions which can be corrected by other means, I prefer to use them because it seems to me that the protracted use of an inlying catheter in the pelvis greatly increases the danger of an intractable infection, particularly normal the ureteropelvic junction is funnel shaped, and contrast agent enters the ureter promptly A good urogram fulfills the above criteria except that the size of the pelvis has not diminished In a poor one, there is persistence or increase of the hydronephrosis, unaltered narrowing at the junction delayed transit of urine down the ureter, or diminution of the renal function

Combining these criteria results were excellent in 44 of the 73 operations, or 60 3 per cent, they were good in 17, or 23 4 per cent and fair in one, or 1 3 per cent Eleven, or 15 per cent were failures

CAUSES OF FAILURE

Several factors are likely to contribute to failure of a plastic operation upon the ureteropelvic junction First of these is an inaccurate estimation of the relationship between the hydronephrosis and the symptoms, which is particularly likely in the patient with small hydronephrosis, so-called "reflex" gastrointestinal symptoms, and an overenthusiastic surgeon It is obvious that widening the outlet of the kidney will not relieve symptoms unrelated to the renal lesion

A second source of error is overestimation of the functional capacity of the diseased kidney, so that a hopelessly injured organ is "repaired" Failure may result either because residual renal tissue is so fibrotic that infection cannot be eliminated, or because the motor mechanism is so impaired (fibrosis or atony) that it cannot propel the urine satisfactorily While the former defect can be estimated with reasonable accuracy by means of preoperative function tests and by inspection at the time of operation, supplemented perhaps by study of a fast frozen section, I know of no satisfactory method of determining the latter except by trial and error

Many errors of technique can cause failure Most easily avoided is the use of nonabsorbable sutures although the relationship between foreign bodies and lithiasis is so well known that this should not occur Neglect to reduce the size of a greatly dilated pelvis may leave such a large pool of urine that infection resists treatment Conversely resection of too much pelvis, accompanied by peripelvic and periureteral fibrosis may cause constriction of the ureter where it is pulled against the lower pole of the kidney, this requires intubated ureterotomy, or it may be irreparable Leaving aberrant vessels anterior to the renal pelvis because it has been possible to anchor them well above the ureteropelvic junction may lead to obstruction of the pelvis itself, as already mentioned Division of accessory vessels which supply an unexpectedly large part of the parenchyma may leave too little functioning tissue to be useful theoretically at least, a clot can be propagated backward from a ligated vein to the main renal vein and cause infarction The ligation of accessory renal arteries has been alleged to cause hypertension, but satisfactory proof is lacking

In my experience another source of failure is the provision of inadequate diversion of the urine during healing either by improper placement of the diverting catheter or by inefficient anchoring so that it slips out prematurely This is readily avoided by the exercise of care at the time an inlying ureteral catheter may save the kidney if the tube slips out tionnaires or to return for followup, leaving 70 individuals with 73 operations for review All of these returned questionnaires, and all but nine returned for examination

Preoperative investigations and findings at operation disclosed the following causes of obstruction at the ureteropelvic junction

Accessory vessels to the lower pole	17
Stricture	16
Neuromuscular dysfunction	14
Vessels and fascial sheet	12
Periureteral scar	6
Postinflammatory polyps	3
Fascial sheet, high attachment of ureter	3
Vessels and stricture	3
Vessels, stricture, and fascial sheet	3
Fascial band	3
Granuloma	1
	81

Complicating lesions present before operation included

Stones not contributing to obstruction	6
Bilateral obstruction	4
Slight ureterectasis	3
Horseshoe kidney	3
Ectopic kidney	2
Solitary kidney (acquired)	2
	20

RESULTS

Assessment of the result of an operation like Y plasty, which is life saving only if the kidney is solitary is not easy except in failures, and depends greatly upon the judgment of the reviewer It is doubtful that any two urologists could review this material and arrive at the same conclusions The criteria used in this review are the degree of subjective relief, the state of the urine, and the findings on urography Results are classified as excellent, good, fair, or as failures In terms of subjective relief "excellent" means complete disappearance of symptoms, "good", that the patient reports occasional mild discomfort on the operated side, "fair", that there has been recurrent nondisabling pain with evidence of infection, and "failure", that relief did not occur and, usually, that a second operation was necessary While 2 patients are perfectly well after secondary operations and a third requires annual ureteral dilatations to be comfortable, these are classed as failures because the original Y plasty failed to achieve its objective

In terms of the urine, "excellent" means clear, sterile urine, "good" refers to the presence of bacteria without pus, "fair" means that a few pus cells are present together with bacteria

There is obviously room for quibbling in interpreting the urograms For our purpose, an excellent urogram is one which shows no impairment of function, the size of the hydronephrosis has diminished and the calyces have returned to

A third patient (1943) developed pneumonia, then thrombophlebitis postoperatively, so that both splint and nephrostomy were left in situ for an inordinately long time, obstruction then recurred and intubated ureterotomy had to be done She was then lost to followup When she returned she had several good sized stones in her solitary hydronephrotic left kidney These were removed and the ureteropelvic junction was adequate, the urine was sterilized with penicillin and streptomycin, and she has remained well despite several pregnancies

Another patient (1948) had a nephrectomy elsewhere in 1950 for a calculous pyonephrosis, details cannot be secured

A stone which did not form postoperatively played an embarrassing part in another failure (1941) A large stone, thought to be solitary, was removed from the left kidney, and Y plasty was done for a stricture She recovered and left the state Within a year she had pelviolithotomy elsewhere, scrutiny of our roentgenograms indicated that this stone was present at the time of the original operation, and had been mistaken for the nucleus of the one which was removed While this has no relationship to the Y plasty, it is a failure This, of course, emphasizes the value of roentgenography at the operating table even when one is sure that the stone is solitary

Each of the remaining patients represents a blunder of a different sort In the first (1936), the urine was diverted by pyelostomy with a Robinson catheter, which slipped out on the third postoperative day It could not be reinserted, and the ensuing extravasation and infection prompted a nephrectomy which would not be considered today

In 2 patients (1941 and 1948) recurrent strictures developed after symphysiotomy for horseshoe kidney, combined with Y plasty A splint was used in the first but not in the second patient The first had another plastic operation elsewhere 7 years after the first one, and now reports herself well The second requires a semi-annual or annual ureteral dilatation to be comfortable, one wonders whether the free trip to the city does not contribute as much to her comfort as does the treatment

In a ninth patient, already mentioned, accessory vessels left anterior to and above the junction caused persisting obstruction which was not relieved by their subsequent removal, and he had to wear a nephrostomy tube in his only kidney for the rest of his life There must have been some element of atony of the smooth muscle of the renal pelvis

A tenth failure (1943) was due to inadequate nephrostomy, the renal pelvis but not the ureter was duplicated Y plasty with nephrostomy in the lower segment was followed by obstruction and infection which could not be corrected, apparently because the communication between the two segments was occluded by postoperative swelling The bacteria were resistant to the feeble antibacterial agents then available and the ensuing pyonephrosis required nephrectomy A nephrostomy in each segment would have prevented this failure

The last one (1942) cannot be explained satisfactorily because the patient refused to return for investigation, but said in the questionnaire that she "would have been better off if she had never had an operation "

Occasionally, without any obvious technical fault, scarring around the junction may produce recurrent obstruction, presumably because of extravasation or postoperative infection

The commonest single cause of failure in my own experience has been postoperative infection of the kidney with an urea splitting bacterium, usually Bacillus proteus Since catheters for urinary diversion and splinting appear to conduct these organisms into the bladder from contaminated bedclothes (Bacillus proteus is a common inhabitant of the colon), this is a powerful argument for the omission of catheters, as suggested by Hamm and Weinberg If they are used, one should try to prevent infection by using antibiotics wisely, it seems reasonable that lithiasis can be discouraged by altering the composition of the urine until it can be sterilized Theoretically worthwhile measures include dilution through diuresis, reduction of phosphate excretion by the administration of aluminum salts (Shorr), and increasing the solubility of calcium by the use of salicylates (Prien) I have yet to see postoperative lithiasis when all of these measures have been used, but more experience is needed to prove their value in this situation

The advent of the modern antibiotics has permitted postoperative sterilization of the urine in most instances in which the patient returns faithfully for followup Of particular value in infections with Bacillus proteus have been combinations of furadantin and chloromycetin with gantrisin

It seems almost superfluous to mention violations of good surgical technique, but perhaps one should refer to such faults as the use of sutures heavier than 0000 chromic, taking large bites of tissue with production of angulation, buckling, or spurs of pelvic wall, inadvertent placement of stitches across the lumen of pelvis or ureter, *et cetera*

ANALYSIS OF FAILURES

Because it is a truism to say that one can learn more from his failures than from his successes, it seems worth while to discuss the former briefly, especially since the incidence is a little higher than is suggested by current reports which, however, contain few details concerning patients followed carefully for long periods Dates indicate the year of operation for orientation in relation to the advent of antibiotics and of adjunctive methods such as the administration of aluminum salts and of salicylates The discussion is not in chronological order

The commonest cause of failure was postoperative nephrolithiasis due to infection with Bacillus proteus In no instance was this organism present prior to operation In the first case (1938), left Y plasty was successful, but the patient returned nine months later with Bacillus proteus in the urine from the right kidney, which was found to contain stones, he died after pelvionephrolithotomy At autopsy the stricture on the operated side was corrected and there was no infection Nevertheless, the organism was introduced via the nephrostomy

In a second instance bilateral nephrolithiasis followed an initially successful left Y plasty in 1943 Bacillus proteus was found before discharge, but could not be eliminated While the stones were successfully removed from the left kidney, the patient could not bring herself to submit to operation on the other side

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COMMENT

It will be noted that three of the four failures due to postoperative lithiasis antedate the appearance of effective antibiotics and of measures designed to dissolve calculi or to alter the concentration of calcium and of phosphorus in the urine, while the fourth one (1948) preceded the advent of the few agents which are reasonably effective against Bacillus proteus The risk of this complication now can be practically eliminated, although it can still occur if the surgeon does not take effective measures during the patient's convalescence, or if he fails to continue treatment until the urine is sterile after there are no antibiotics in the urine Whether the techniques advocated by Hamm and Weinberg will obviate the need for such precautions remains to be seen

Having experienced the complications due to technical errors, none of which was evident at the time of their commission, I doubt that they will be repeated The possibility of recurrent or of postoperative strictures will always be with us, although the use of the potent antibiotics should lessen this danger as well

The prevention of diagnostic errors is merely a matter of stopping to think before operating, and of curbing the tendency to operate while in doubt about the accuracy of the diagnosis

Removing one stone while missing another cannot, of course, be condoned, especially since the means of prevention have been available for so long

SUMMARY AND CONCLUSIONS

Seventy patients with seventy-three Y plasties were followed for from 5 to 24 years after operation

Results were acceptable in 61, or 83 7 per cent, fair in one (1 3 per cent), and were failures in 11, or 15 per cent

The commonest single cause of failure was postoperative lithiasis due to uncontrollable infection by Bacillus proteus, which should now be largely preventable

Other causes of failure include errors in surgical technique, and mistakes in diagnosis, also preventable with a little care

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BILATERAL URETERAL OBSTRUCTION BY RETROPERITONEAL INFLAMMATION

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In 1948 Ormond[1] described an interesting and previously unrecognized syndrome of bilateral ureteral compression by a retroperitoneal inflammatory reaction He presented observations made on two patients, each having complete obstruction of the ureters as a result of encompassing non-malignant retroperitoneal tissue Both patients had a history of chronic illness, weight loss, back and flank pain, oliguria, azotemia, and finally, anuria Since Ormond's report, six additional cases have appeared in the literature [2-7] The case reported herein constitutes the ninth, and is unique in that there was a 4-month interval between involvement of each ureter

CASE REPORT

H C H, V A Hosp No 11782, a 44-year-old white man, was admitted to the hospital on January 18, 1955, complaining of left flank and left lower abdominal pain of 6 months duration He had also noted progressive constipation, vomiting, and gradual weight loss of 40 pounds Cholecystectomy had been performed at another hospital 6 months prior to admission, and subsequent barium studies of the colon and small intestine, and excretory urogram were reported as within normal limits

Physical examination Blood pressure was 130/70, temperature 98 6 There was evidence of marked dehydration and exquisite tenderness in the left flank and left upper quadrant of the abdomen

Laboratory findings Urinalysis showed 8–10 white blood cells per high power field Hemoglobin was 13 6 gm per cent The blood urea nitrogen was 15 mg per cent and urine culture was negative

Course in hospital An excretory urogram performed on admission revealed prompt excretion of dye from the right kidney and outlined a duplication of pelvis and ureter At no time in the study was there evidence of excretion from the left kidney A catheter passed up the left ureter encountered resistance at a distance of 22 cm from the ureteral orifice, and a rapid drip of urine was obtained Retrograde pyelograms (fig 1, *A*) demonstrated mild hydronephrosis, an apparent kink in the ureter at the level of the third lumbar vertabra, and pelvic retention of dye at one hour

On February 3, 1955, the left retroperitoneal space was explored through a

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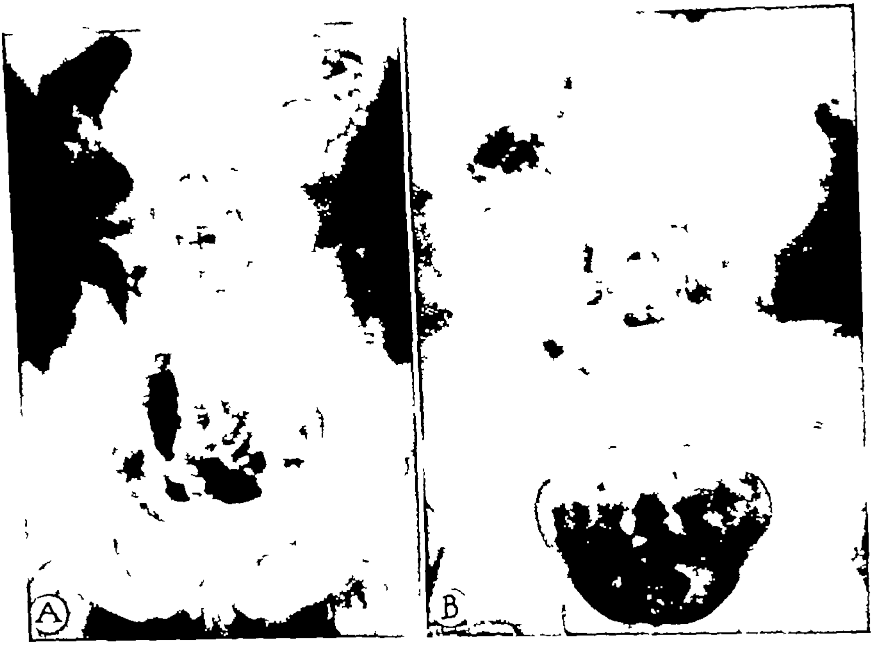

FIG 1 A, retrograde pyelogram demonstrating obstructed, nonfunctioning left kidney *B*, urogram 2 months after operation Excellent function of both kidneys

flank incision The ureter was completely encompassed by an envelope of thick, fibrous, indurated tissue from a point 4 cm below the ureteropelvic junction to the level of the iliac vessels There was no apparent cause of the inflammatory process The periureteral tissue was incised, and a portion taken for histologic study The ureter was then dissected free of this tissue, and intubated with No 240 polyethylene tubing A pyelostomy was performed to divert the urine The splinting tube was removed in 4 weeks, and the pyelostomy tube one week later

An excretory urogram 2 months after operation (fig 1, *B*) revealed excellent function of the left kidney, with minimal, if any, dilatation of the collecting system

The patient was asymptomatic for 4 months after the operation on the left ureter On June 6, 1955, he was readmitted because of right flank and upper abdominal pain of 3 days' duration There was moderate tenderness in the right flank and in the right upper abdomen Urinalysis revealed 8–10 white blood cells per high power field The blood urea nitrogen was 18 mg per cent An excretory urogram (fig 2, *A*) showed no function of the right kidney The left pyelogram appeared normal Retrograde pyelogram (fig 2, *B*) revealed moderate hydronephrosis on the right, with retention of the dye at one hour

On June 30, 1955, the right retroperitoneal space was explored through a flank incision The upper third of the duplicated ureter was dilated, apparently because of obstruction by an envelopment of firm, indurated, periureteral tissue which involved an area 5 cm in length proximal to the iliac vessels This tissue

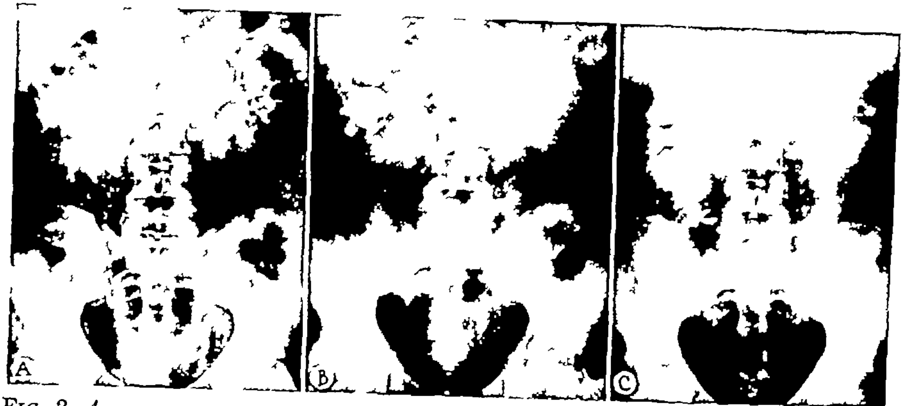

Fig 2 *A*, urogram at time of second admission No visualization of right kidney *B*, right retrograde pyelogram demonstrating dilatation of collecting system and retention of dye *C*, urogram 6 months after second operation Excellent function bilaterally, minimal dilatation of right collecting system

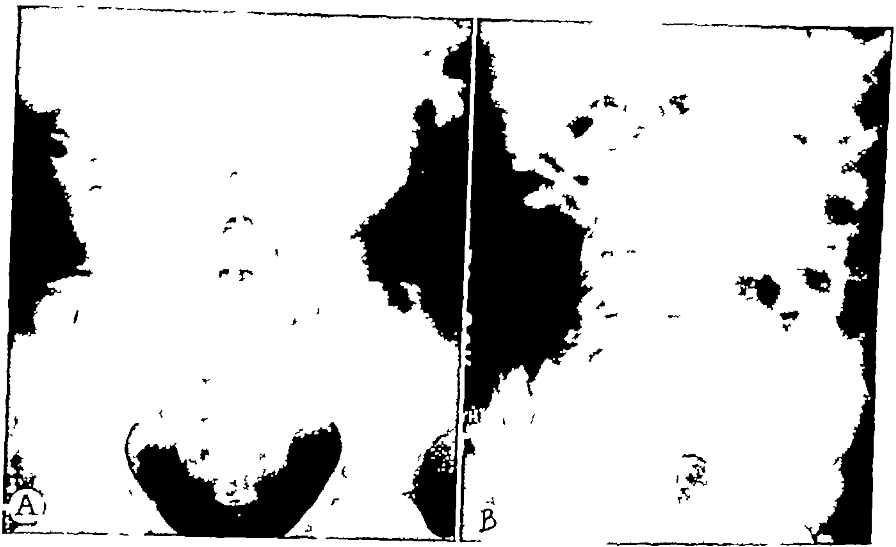

Fig 3 *A*, urogram at time of third admission Non visualization of left kidney *B*, urogram 2 weeks after colostomy Excellent function of both kidneys

extended medially towards the aortic bifurcation and beyond the confines of the operative field Incision and biopsy of the periureteral tissue were performed, and the involved segment of ureter completely freed from the constricting envelope The duplicated ureter fused at the level of the iliac vessels The involved area was intubated, and diversion of the urine accomplished by proximal ureterostomy in situ The splint was removed in 4 weeks, and the ureterostomy tube 5 weeks postoperatively An excretory urogram (fig 2, *C*) 6 months after operation revealed excellent function bilaterally and minimal right hydronephrosis The patient was asymptomatic at this time, and had gained 40 pounds in weight

Two and one half months later the patient was readmitted with symptoms of constipation, ribbon stools, and abdominal distension Studies demonstrated

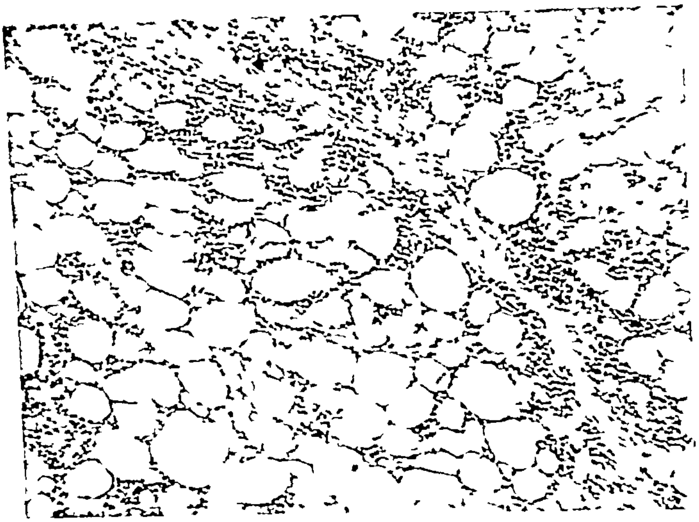

FIG 4 Histological section of periureteral tissue Nonspecific chronic inflammatory changes

a constricting lesion in the colon just above the rectum There was no apparent function of the left kidney on urogram (fig 3, *A*)

Exploratory laparotomy revealed no evidence of mesenteric adenopathy or intra-abdominal metastasis The rectosigmoid just at and below the peritoneal reflection was involved in a large inflammatory process and was markedly adherent to the sacrum The retroperitoneal tissues showed evidence of chronic inflammatory reaction Biopsies of the retroperitoneal tissues, bowel, and mesentery disclosed chronic inflammatory reaction only, with no evidence of malignancy A proximal colostomy was made because it was impossible to mobilize the bowel for resection Two weeks postoperatively function had returned to the left kidney, and both pyelograms were normal in appearance (fig 3, *B*) Normal pyelograms were again noted 5 months later

Histologic examination of the tissue from the periureteral region (fig 4) showed fibro-fatty tissue with chronic inflammatory reaction The majority of the cells are of the mononuclear variety Few neutrophils are in evidence In several areas the inflammatory cells are clustered around vascular channels

DISCUSSION

The periureteral inflammatory reaction in this patient apparently was caused by a septic process in the region of the rectosigmoid colon The exact etiology cannot be ascertained, but perforation of the bowel wall by a foreign body, or diverticulitis, are likely possibilities The alternating and recurrent ureteral obstruction presents an even greater enigma Exacerbations and remissions of the initiating process deep in the pelvis, or alterations in the lymphatic drainage in the retroperitoneal space by the ureterolysis might be responsible

This case emphasizes the necessity for a careful search for the initiating lesion in patients presenting the syndrome Only by proper treatment of the primary cause of the retroperitoneal inflammation can a successful outcome be assured If such a primary lesion cannot be found, ureterolysis, splinting of the involved area, and proximal diversion of the urine appear to offer a reasonable method of treatment of the urinary tract problem

SUMMARY

The ninth case of bilateral ureteral obstruction by retroperitoneal inflammation is reported

The clinical picture, pathogenesis and management are discussed

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MANAGEMENT OF THE SEVERED URETER

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Because of its sheltered anatomic position, rarely is the ureter injured by external blunt trauma. Sharp instruments or penetrating missiles can perforate or completely sever it. More frequently, injury results from extensive surgical procedures, such as radical hysterectomy An actual perforation of the ureter is not required, ureterovaginal fistula has followed extensive damage to the adventitia with impairment of its blood supply Such unfortunate results are not uncommon, Masterson[1] reported 11 instances of ureterovaginal fistulas following 105 radical hysterectomies with lymph node dissection Trauma to the ureter has followed abdominoperineal resection for carcinoma of the lower sigmoid and rectum Also, intrinsic disease of the ureter, such as tumor or a retrocaval position, may require anastomosis of the severed ends

The results of end-to-end anastomosis of the ureter, as with other small tube-like structures, have not been uniformly satisfactory Thomas D Moore,[2] probably the most outspoken in this respect, states, "through the years much experimental work has been done and numerous methods of performing end-to-end and end-in-end repair of the ureter have been described, the immediate results of which are often most encouraging, unfortunately, however, in the majority of cases, stricture of the site is almost inevitable "

The variety of techniques recommended is also evidence enough that no method has been very successful (fig 1) [3] Arthur Cathro,[4] in an operation for retrocaval ureter, chose to divide the vena cava and reanastomose it rather than divide the ureter He also analyzed 18 reports of end-to-end anastomosis of the ureter (for retrocaval ureter) reported in the literature and he found that only four of the 18 patients obtained satisfactory results Nor has experimental work on animals yielded good results A summary of recent work concerning transection and surgical repair in dogs is included in table 1

We believe the outlook for restoring the continuity of the ureter need not be so gloomy provided certain principles are observed [5] At least it can be tried with a reasonable chance of success Nephrectomy may be done at a later date if necessary

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass , June 4-6, 1956

Acknowledgement is made to the Winthrop Laboratories for their generous supply of hypaque solution, the contrast medium used to obtain the canine intravenous urograms

[1] Masterson, J G Analysis of 105 radical hysterectomies and pelvic lymph node dissections performed in treatment of uterine malignancy In press, Am J Obst & Gynec

[2] Moore, T D Surgery of the Ureter In Urology, edited by Campbell Philadelphia W B Saunders Co , 1954, vol 3, sect 15, chapt 4, p 1864

[3] Textbook of Genito Urinary Surgery, edited by H P Winsbury-White Baltimore Williams & Wilkins, 1948, p 206

[4] Cathro, A J Section of inferior vena cava for retrocaval ureter A new method of treatment J Urol , 67 464-475, 1952

[5] Hamm F C and Weinberg, S R Experimental studies of regeneration of ureter without intubation J Urol , 75 43-51, 1956

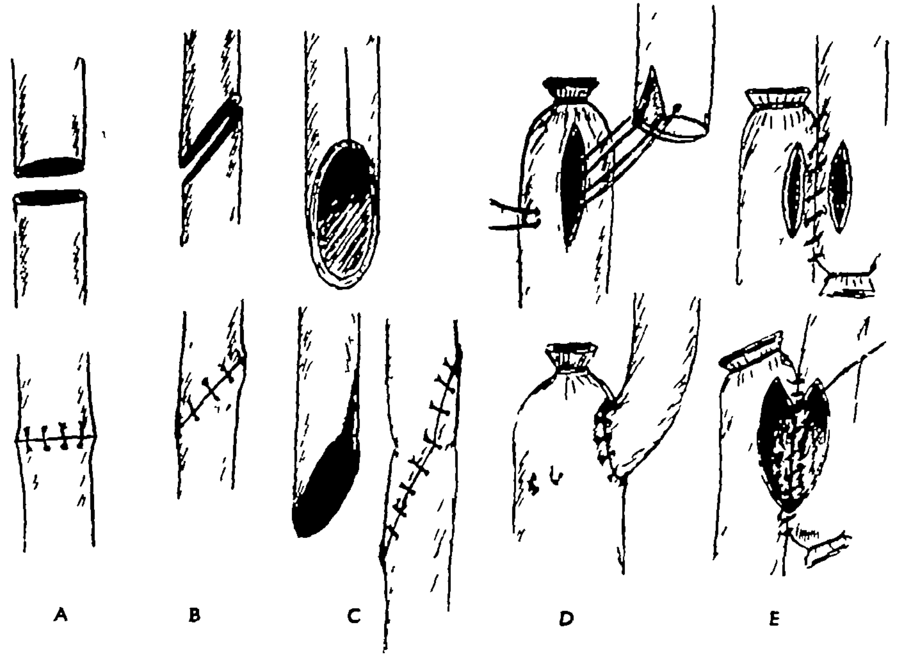

Fig 1 *A*, transverse end to end anastomosis of ureter *B*, oblique end-to-end anastomosis of ureter *C*, oblique end to end anastomosis with longitudinal split of obtuse side *D*, end to end anastomosis with longitudinal split of upper segment on one side *E*, side-to side anastomosis of ureter From Textbook of Genito Urinary Surgery, edited by *H P* Winsbury-White Baltimore *Williams and Wilkins, 1948*

In the event that the ureter is transected, a serious interference with the physiology results, peristaltic waves originating in the proximal segment proceed to the severed level and stop, nor will they traverse the recently sutured ends In the severed ureter a peristaltic wave may therefore encounter a contracted segment below the point of anastomosis A dilatation of the proximal segment is the rule for the first week or two, following end-to-end anastomosis, without diversion of the urinary stream above the site However, after healing without cicatrix is complete, synchronous peristalsis is resumed

Dilatation of the proximal segment means increased pressure and under these circumstances it is unlikely that any type of suture will result in a watertight anastomosis Therefore we have not attempted to effect a watertight closure, but have used fine atraumatic, everting, interrupted mattress sutures designed to approximate the mucous membrane primarily and not allow fibrous tissue to interpose between the joining epithelium Pressure on the suture line is relieved by making a linear incision well above the site of anastomosis (fig 2), drainage is provided by rubber tissue for a minimum period of 9 days or until urinary drainage ceases Our experimental work emphasizes the importance of maintaining adequate drainage

Another important principle to be observed in restoring the continuity of a small tube-like structure, is a type of anastomosis that will increase the circum-

TABLE 1

Name of Investigator and Reference	No of Dogs Used	Procedure and location of Anastomosis	Type of Anastomosis	Results
Marion, H J d'urol , 27 273, 1929	8	Junction of lower and mid third	End to end, 4 denuded, 4, hot needle to mucosa	All strictured at point of suture
Bump, W S and Crowe, S Surg , Gynec & Obst , 49 346–351, 1929	26	Catheters removed in 8–14 days Catheters for diversion of urine Mid ureter anastomosis	Transverse end to end	6 died of post op infection 6 successful with good condition of kidney and normal histologic appearance of anastomosis
Iselin, M Surg , Gynec & Obst , 49 503–509, 1929	12	Accompaning pyelostomy Solid bougie splinting of ureter	Transverse end to-end	5 died of peritonitis, infection always present Peristalsis observed to be very slow
Hryntschak, W Ztschr f urol chir , 42 268, 1936		Nephrostomy used and ureters splinted	Transverse to end	Histologic examination fibrosis at site Majority of dogs died of peritonitis or urinary extravasation 2 had good functional results, except for hypertrophy of ureter
Wildbolz, E Ztschr f urol chir , 42 56, 1936	6	Reanastomosis with circular continuous suture	Transverse end to-end	Good results in seen 2 years later Believe good results a matter of technique, but dilatation noted above suture line
Kramer, S E Surg , Gynec & Obst , 46 217–220, 1928	3	Mid ureter, catheters to pelvis and across anastomosis	Transverse end to-end	All had stricture at site of anastomosis
Davalos, A J Urol , 58 22–27, 1947	18	Mid ureter	Continuous everting mattress suture	Good results in 1 dog 7 months postoperatively

TABLE 1 *Continued*

Name of Investigator and Reference	No of Dogs Used	Location of Anastomosis	Type of Anastomosis	Results
Sutherland, C G, Brown, W E, Atkinson, J C and Birmingham, R T South Med J, 47 525–530, 1954	6	1″ of lower third of ureter resected, polyethylene catheter bridged the gap and passed into bladder	No suture	All strictured after gap in ureter healed by *filling in with fibrous* tissue
	4	Lower third severed transversely and ureter intubated with polyethylene catheter	End to-end anastomosis	Catheter removed 4th day Result in 10 days, incomplete healing on 38th day Stricture mild to complete
Weisman, J L Brit J Urol, 6 11–26, 1934	9	Extraperitoneal anastomosis done close to insertion of ureter into bladder, No 4 or 5F urethral catheter as splints	Transverse incision, end to-end	5 dogs had good lumen, stricture formation and urinary extravasation in 4 dogs

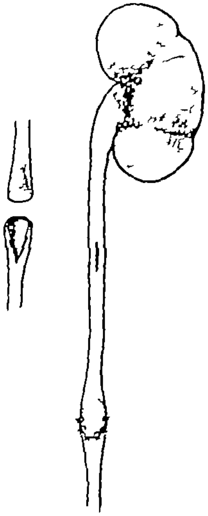

FIG 2 Anastomosis with everting mattress stitch

ference A Z type of anastomosis has been advocated by Holman (fig 3),[6] and Anderson and Hynes (fig 4)[7] have devised a novel method of anastomosis The simplest and most satisfactory method of increasing the diameter of the ureter

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[6] Holman, E and Hahn, R Application of Z plasty technique to hollow cylinder anastomoses Ann Surg, 138 344–349, 1953

[7] Anderson, J D and Hynes, W Retrocaval ureter Brit J Urol, 21 209–214, 1949

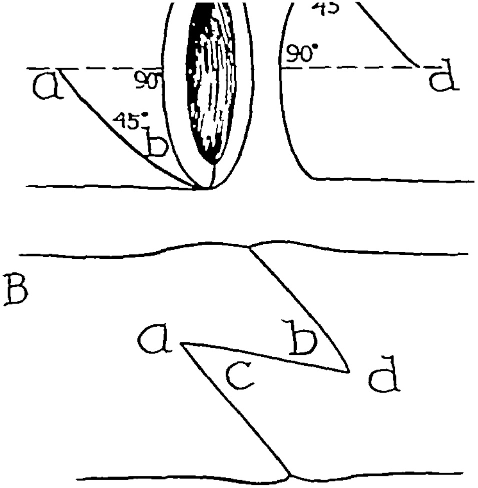

Fig 3 Principle of Z-plasty as applied to end-to-end union of blood vessels parallel incisions *a b* and *c d* are made permitting approximation of *a* and *c*, *b* and *d*, with definite increase in circumference at site of anastomosis (After Holman [6])

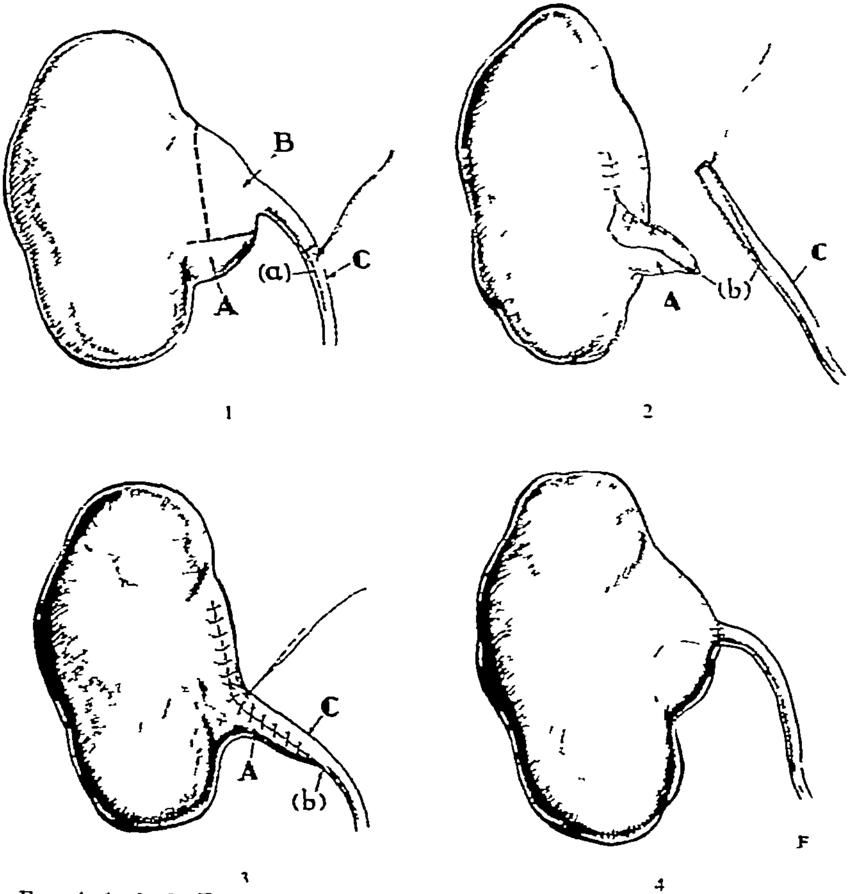

Fig 4 *1*, *2* 3, Type of ureteropelvic anastomosis, as advocated by Anderson and Hynes *4*, Type of anastomosis that is prone to produce circular scar and subsequent stricture formation

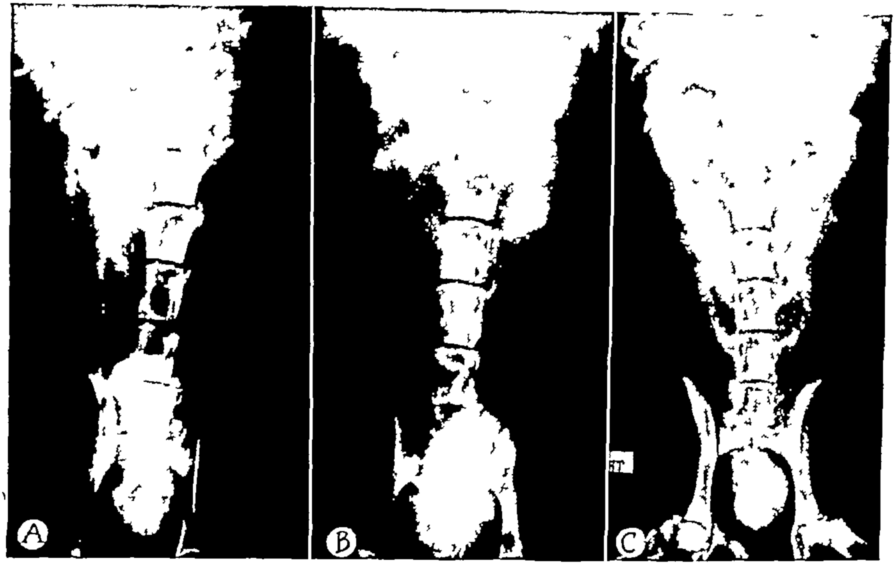

FIG 5 *A*, dog No 349 *Bilateral ureteroureteral anastomosis* Right *visible, 10 months* postoperatively, left, 8 months postoperatively
B, dog No 525 Solitary kidney, 3 months postoperatively
C, dog No 554 Right *anastomosis* 5 months postoperatively

is simply to incise each end for a distance of about one centimeter, as described by Nesbit[8] in his ureterointestinal anastomosis and join the spatulated ends with fine everting chromic catgut No splinting tube or catheter has been required

RESULTS

Clinical Patients who require this type of surgery are seen infrequently, only one human subject, a man (M S 44 years, Kings County Hospital No 88,986) had a repair of a ureter with spatulated end-to-end anastomosis His ureter was severed while undergoing ligation of inferior vena cava in April 1955, on the general surgical service, University Division, Kings County Hospital No diversion of the urine above the site of the anastomosis was done Some dilatation of the proximal segment was present for over six weeks A urogram taken during the twelfth postoperative week indicated that the dilatation had subsided and the pyelogram was almost normal He has been followed for 13 months with no symptoms referable to his right kidney and no instrumentation has been required

Experimental Twenty anastomoses were done in 16 dogs, 4 dogs had both ureters divided and joined Of the 16 dogs, four died of distemper in from two to six days postoperatively including one dog with bilateral anastomosis Autopsies were performed on all four, the site of anastomosis was satisfactory Of the remaining 12 dogs, five died of urinary extravasation as a result of pulling or chewing out the drain before healing had taken place In four of the 5 dogs, the drains were chewed out on or before the sixth day, in the fifth, it was removed on the ninth day postoperatively and the dog died on the eleventh day

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[8] Nesbit, R M *Ureterosigmoid anastomosis by direct elliptical connection, preliminary report* Univ Hosp Bull, Ann Arbor 14 45, 1948

This dog had a bilateral anastomosis, at autopsy a calculus and obstruction were noted in the right kidney (operated upon 3 months previously) Autopsy on the other dogs in this group indicated that they died of urinary extravasation and infection

The 7 dogs remaining are still alive from 2 to 11 months postoperatively Two had both sides operated on, making a total of nine anastomoses (fig 5, A) In one animal the first anastomosis was a failure resulting in a pyonephrotic kidney This was removed and the solitary ureter was severed and anastomosed This dog is still alive and well (fig 5, *B*) A second obtained a poor result but retains good function and appears healthy The remaining seven anastomoses in six dogs appear to be functioning well and the dogs are healthy (fig 5, *C*)

The results in the human subjects should be better than those in the dog

The importance of maintaining adequate drainage until the ureter is healed cannot be too strongly emphasized In those animals where the drain came out prematurely with marked fibrosis of the ureteral tissues, constriction of the ureter or death occurred rapidly due to wide extravasation

SUMMARY

Satisfactory results were obtained in seven of 9 operations on 7 dogs, where the ureter was severed and reanastomosed using a vertical slit in each end to produce a spatulated effect, thereby increasing the caliber of the ureter at site of anastomosis The suture was a fine chronic everting stitch The urine was diverted by a linear incision made well above the site of anastomosis no splinting catheter was used

We feel safe in recommending this operation, although it has only been used in 1 patient Here, the technique of anastomosing the spatulated ends of the ureter was used without the ureterotomy above the site of anastomosis He is living 13 months without complaints referable to his kidney, ureteral dilatation or instrumentation has not been required

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A NEW OPERATION FOR URETERAL ECTOPIA CASE REPORT

THOMAS E GIBSON

A review of the literature in 1949 by Burford, Glenn, and Burford[1] revealed that 425 cases of ureteral ectopia had been reported To report an additional case of a condition which has been so thoroughly covered would be needlessly repetitious were it not possible to contribute a new note to some phase of the problem It is hoped that the surgical management of the case herein reported may occasionally find useful application

CASE REPORT

A 17-year old girl gave a history of incontinence since birth Urological studies at the age of 2, 9, 11, 15 and 17 years had failed to elucidate the cause She came to my office with a set of excretory urograms which appeared normal (fig 1, *A*) Her incontinence was worse in the daytime than at night She and her parents were becoming desperate because she was soon to graduate from high school and wished to pursue a nursing career Suspecting an ectopic ureteral orifice from the history, my first procedure was to carefully inspect the vulva and at the same time make sudden pressure on the lower abdomen over the bladder region This caused a spurt of clear urine to come from a small hidden opening in the vestibule between the urethra and vagina A 6F olive-tip ureteral catheter was passed into this opening as far as it would go (4–5 cm) and injected with neo-iopax revealing a dilated ureter extending upward toward the right kidney (fig 1, *B*) Even with forcible injection, it was not possible to fill it above its midportion The lower part of this anomalous ureter apparently terminated in a Gärtner's duct Here, there were associated diverticula and sacculations resembling somewhat the morphology of a seminal vesicle (fig 1, *B*) * From a knowledge of embryological developmental anomalies, the natural assumption was that we were dealing with a supernumerary ectopic ureter leading to the upper pole of a double right kidney, although the excretory urogram gave no intimation that such was the case The right kidney was exposed through the usual right flank incision and the diagnosis was confirmed as shown in the composite drawing (fig 2) Our intended plan of attack was to perform a right heminephrectomy and remove as much of the ureter as possible through this incision However, this proved to be impractical for two reasons First, the kidney resembled a normal healthy single organ and, second, the renal pedicle was anomalous, entering the kidney near the upper pole so that a partial nephrectomy was not feasible A total nephrectomy was then considered but rejected because the idea of re-

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Read at annual meeting of American Association of Genito-Urinary Surgeons, *Osterville*, Mass , June 4–6, 1956

[1] Burford, C E , Glenn, J E *and* Burford, E H *Ureteral ectopia* A review of the literature and 2 case reports J Urol , 62 211–218, 1949

* As early as 1882, Kocks[2] stated that the paravaginal portion of the wolffian duct persists in 80 per cent of women He stated that from the distal end there develops occasionally an outgrowth in the form of a sacculated diverticulum which is known as "Schüller's gland", and it is the homologue of the *seminal vesicle*

[2] Kocks, J Ueber die Gartner'schen Gange beim Weibe Arch f Gynakol , 20 487–491, 1882

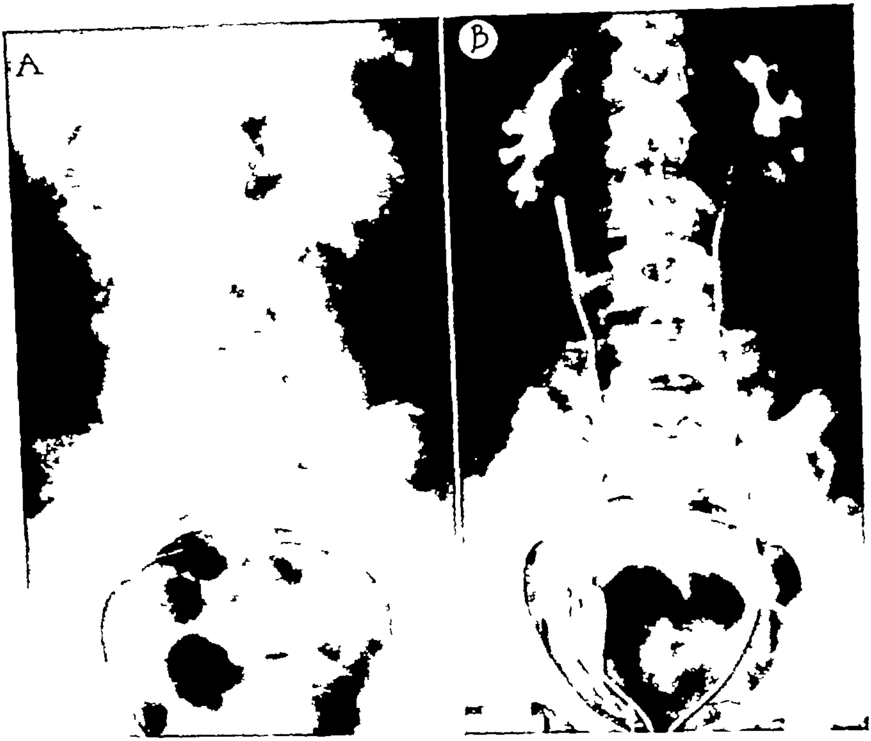


FIG 1 *A* excretory urogram reveals apparently normal upper urinary tract, although on right side there exists a double kidney with complete reduplication of ureter and ectopic ureteral orifice opening in vulva between orifices of urethra and vagina

B, ectopic ureteral orifice opening in vulva was revealed by making sudden pressure over bladder region This caused a jet of clear water to spurt from a small, almost invisible orifice situated between the urethral and vaginal orifices A 6F ureteral catheter could be passed about 5 cm Forcible injection of neo iopex outlined a greatly dilated tube extending upward toward right kidney It was impossible to inject the ectopic ureter in its upper portion It apparently opened below in a vestigial Gärtner's duct containing sacculations or diverticula (Schüller's gland)

moving a normal kidney was repellent Therefore, after excision of as much of the ectopic ureter as could be reached the upper pelvis was anastomosed to the lower pelvis as shown in figure 3 The patient had a smooth convalescence and was discharged from the hospital on the tenth postoperative day A retrograde pyelogram 3 months later showed a satisfactory result (fig 4) The patient has remained dry and symptom-free now for more than a year, and both patient and parents are extremely happy over the result

COMMENT

One may wonder why such a comparatively simple solution to the problem of supernumerary ectopic ureter has not been utilized in the past However, upon reviewing the literature it soon becomes evident that such treatment is not feasible in most cases for obvious reasons Usually the ectopic ureteral orifice leads to a tremendously dilated ureter capped by a segment of kidney that is not only chronically infected, but has also undergone hydronephrotic atrophy so

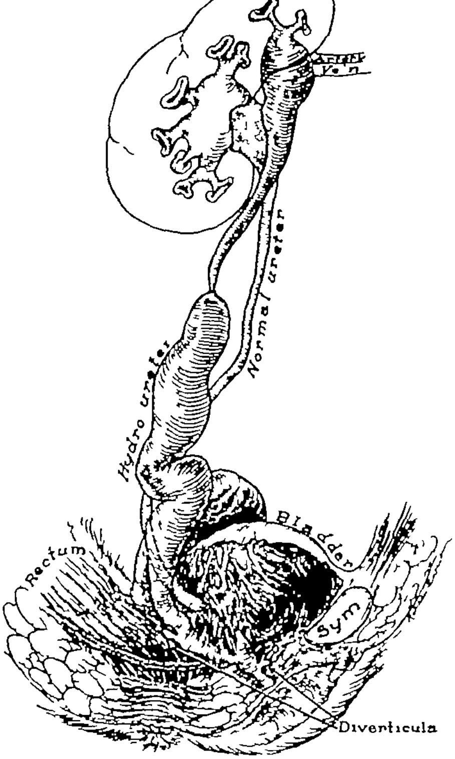
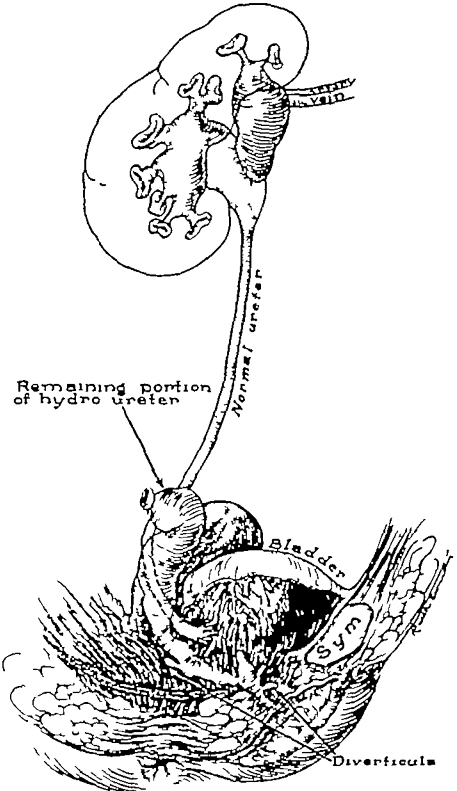


Fig 2 Composite sketch of findings as revealed by pyelography and surgical exploration Ectopic ureteral orifice opening in vestibule between urethra and vagina and arising from upper pole of kidney



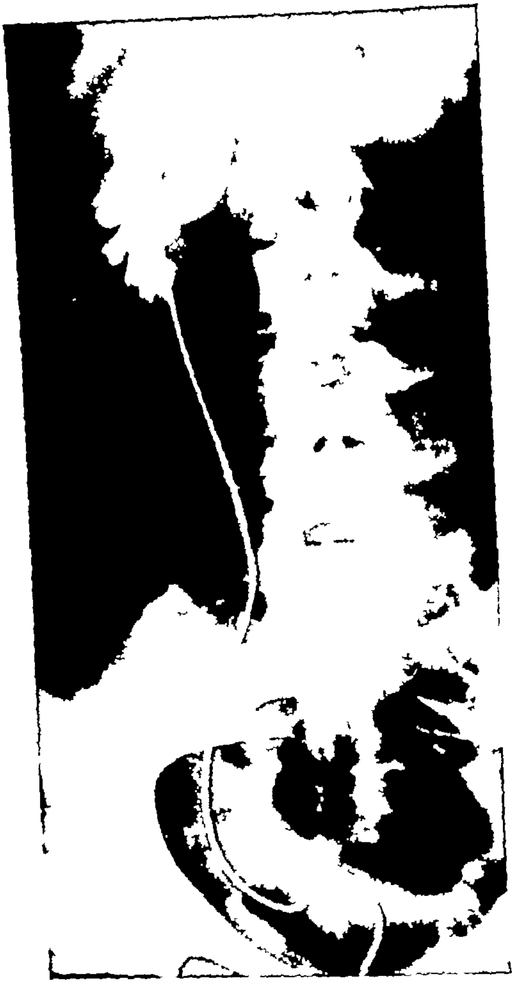


Fig 4 Retrograde pyelogram 3 months postoperatively shows satisfactory result Patient has had no further symptoms

that it is functionally worthless In addition, the renal pedicle is usually so situated that heminephrectomy is comparatively easy

In a series of some 40 cases, Campbell's[3] treatment consisted routinely of heminephrectomy and removal of as much of the dilated ureter as could be comfortably reached through a flank incision The terminal segment of ureter was left behind and does not appear to have been a source of subsequent morbidity Less favored procedures have been 1) partial removal of the ureter with ligation rather than heminephrectomy, 2) ureterocystostomy, 3) excision of the entire ureter with heminephrectomy, and 4) in the milder forms of ectopia in which the ureter opens in the urethra, the orifice has been incised backward so as to open in the bladder thereby becoming subject to sphincter control The latter

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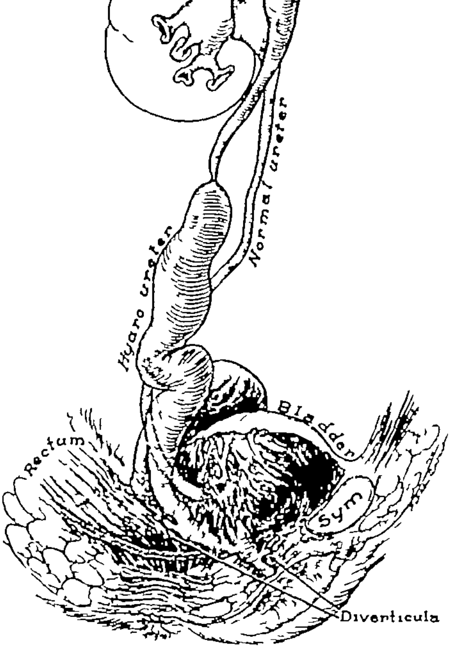
[3] Campbell, M F Urology Philadelphia W B Saunders Co , 1954, vol 1, pp 314–324



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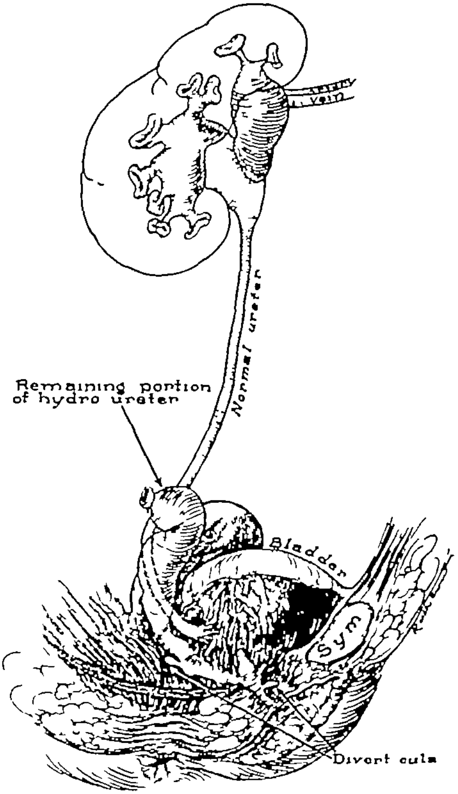
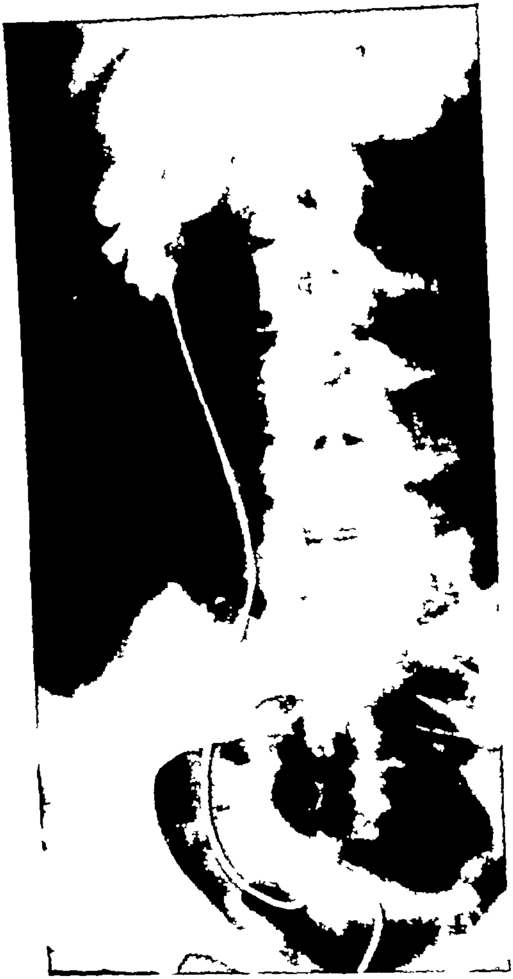


FIG 3 Because of normal appearing kidney and renal pedicle that entered hilus near upper pole, upper pelvis was anastomosed to lower pelvis and lumbar portion of ectopic ureter removed



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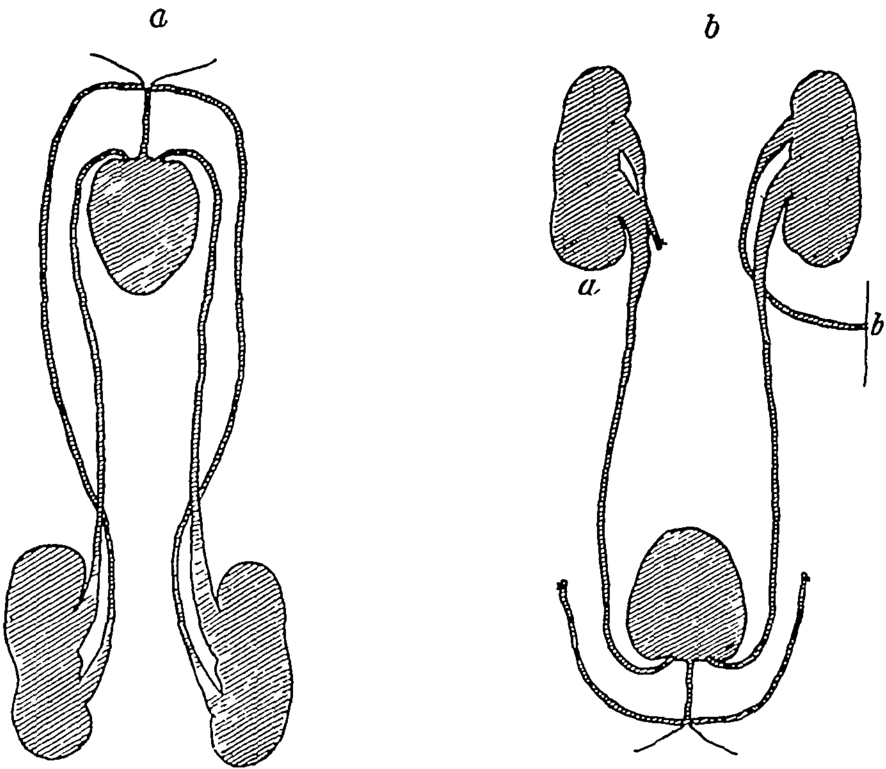

FIG 5 Bilateral ureteral ectopy reported by Kümmell and Graf, illustrating their method of treatment

procedure is mentioned by Kelly and Burnam[4] as having been practiced by Hunner fifty years ago The other procedures above mentioned are obviously more hazardous than that recommended by Campbell

Search of the literature has revealed an interesting case report by Kümmell and Graf[5] of a fifteen-year-old girl with four ureters, two opening normally in the bladder and two opening in the vagina On the right side anastomosis of the two pelves was done (fig 5) and later the left ectopic ureter was treated by cutaneous ureterostomy Thom (1928) in a review of 186 cases cites 1 instance of anastomosis between the two pelves of a double kidney Eisendrath (1938) in a review of 255 cases cites 1 case by Haselhorst in which the ectopic ureter was ligated and anastomosed to its fellow on the same side

Aside from cases with ectopic ureteral orifices, there have been several instances of successful anastomosis of one ureter to another, either homolaterally or contralaterally In a recent personal communication, Deming cites 2 cases of highly malignant bladder tumors in which he successfully anastomosed the ureter on one side to its mate on the opposite side The first successful anastomosis in the living human of a ureter on one side to its mate on the opposite side was reported before this Association by Higgins in 1934 under the term, "Transuretero-ureteral anastomosis." Moore in 1948 collected eight such cases including one of his own, all successfully done with no mortality. Moore's comprehensive paper also includes the personal report of a successful operation, done for the first time, consisting of transureteropyelostomy in which the ureter of a left ectopic kidney was anastomosed to the pelvis of the opposite ectopic kidney.

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[4] Kelly, H A and Burnam, C F Diseases of the Kidneys, Ureters and Bladder New York D Appleton & Co , 1914, vol 2, pp 34–341

[5] Kümmell, H and Graf, H Handbuch der Praktischen Chirurgie, 5th ed , vol 4, pp 385–6 (Garre, Kuttner und Lexer)

Such procedures would be preferable to cutaneous ureterostomy or uretero-intestinal implantation in cases where transplantation of one ureter has become necessary.

CONCLUSION

In supernumerary ectopic ureter, partial excision of the ureter with anastomosis of the upper pelvis to the lower pelvis is recommended provided the upper pole of the double kidney has not been destroyed by infection and hydronephrotic atrophy.

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USE OF CLORPACTIN WCS 90 FOR RELIEF OF SYMPTOMS DUE TO INTERSTITIAL CYSTITIS

WM NILES WISHARD, JR , MYRON H NOURSE AND J H O MERTZ

From the Department of Urology, Indiana University School of Medicine and Methodist Hospital, Indianapolis, Ind

Interstitial cystitis has been the happy hunting ground of therapeutics since Hunner first described the lesion in 1915 It has been locally treated by segmental or subtotal resection, electrocoagulation, overdistention, instillation of 2 per cent silver nitrate and injection with alcohol, cortisone etc Systemic treatment has included the following drugs neoarsphenamine, urinary antiseptics, emetine, cortisone and probanthine So far as I am aware no one has ever reported any predictable certain method of cure The best that can be said is that the symptoms may be alleviated

Overdistention and instillation of 2 per cent $AgNO_3$ has been the most acceptable method of relief in our hands until O'Conor[1] reported the use of clorpactin WCS 90 at the 1955 meeting of the North Central Section of the American Urological Association Infected with his enthusiasm, we at once obtained a supply of the preparation from the Guardian Chemical Corporation of Long Island City, N Y and wish to report on our results

Clorpactin[2] is a generic term for closely related, highly reactive chemical compositions having a modified derivative of hypochlorous acid in a *buffered* base Its bacteriocidal potency is similar to that of elemental chlorine without the latter's toxicity or destructive effect on tissue cells Clorpactin vapor is as effective as the solution It is a white soluble powder which is stable in the refrigerator but should be used within a few hours after mixing with water Two grams are dissolved in 1000 cc tepid water Tap water may be used but we have found distilled water gives a clearer solution The solutions are germicidal, fungicidal, viruscidal, nontoxic and nonirritating in therapeutic doses The activity of clorpactin is dependent upon the liberation of hypochlorous acid and to its oxidizing effects, wetting and penetrating properties and detergency The material is highly buffered, its pH 6 5 It also deodorizes Chemically it is monooxychlorosene whose active chlorine content is about 4 per cent The label on the box reads "active chlorine derived from calcium hypochlorite " Its phenol coefficient is 27 [3] It should be mixed in glass or ceramic containers It will not injure stainless steel but will oxidize copper or other metal surfaces A 0 28 per cent solution kills tetanus spores in 5 minutes A 0 5 per cent solution in 1 minute makes tubercle bacilli harmless to guinea pigs A 1 12000 solution kills Endamoeba histolytica in 48 hours It is bacteriocidal to common bacteria exposed for 1 5 minutes in 1 5000 dilution [3] It will kill cultures of Staphylococcus aureus in a few

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville Mass , June 4-6, 1956

[1] O'Conor V J Clorpactin WCS 90 in the treatment of interstitial cystitis Quarterly Bul N W U Med School 29 392, 1955

[2] Clorpactin Guardian Chem Corp pamphlet

[3] Swanker, W A Use of clorpactin WCS 90 as an antiseptic in surgery Am J Surg , 90 44, 1955

seconds It has wide range antibacteriocidal action, no serious side effects and organisms do not develop resistance to it

Clorpactin WCS 90 is used in dermatology for athlete's foot, psoriasis and acne, WCS 60 in oral and dental hygiene, WCS 90 in body cavities, wounds, bladder, renal pelvis and fistulas, XWCS in massive or deep infections, CXB in the vagina, and 2 DC for sterilization of instruments CXW is being studied for aerosol application The preceding are used topically

Zwerling[4] has used clorpactin with marked improvement in the treatment of pharyngitis, globus hystericus, canker sore and oral antral fistula Swanker[3] reports its usefulness in wet dressings on skin grafts and for prevention of stitch abcess Lattimer[5] first used it in the bladder with beneficial results in healing tuberculous ulcers which had not responded alone to streptomycin PAS and INH He found that tuberculous ulcers responded in 2 weeks to the use of 0 2 per cent solution of clorpactin WCS 90 every 3 days More frequent use caused hematuria He recommends 60 cc instilled in the bladder 1 minute, with 5 interchanges of the solution, and found that bladder capacity increased although permanent scarring was not absorbed

O'Conor[1] first used clorpactin WCS 90 for interstitial cystitis He overdistended the bladder for 1 minute weekly for 4–5 weeks in chronic longstanding cases, finding that bladder capacity increased while symptoms decreased He also believes that it would be of help in clearing up sloughing or ulcerative lesions of the bladder

We first used clorpactin WCS 90 in October 1955, dissolving 2 gm of the powder in 1 quart of tap water This gives a slightly turbid solution with foam on the surface Later we used tepid distilled water, pouring the powder on the water, and found that it dissolved faster and gave a clear solution We have always used the solution within an hour or two after it is made up The powder is kept in a refrigerator Frequently the entire quart is not used and the remainder is discarded Inasmuch as the material is somewhat expensive we have found it more economical to weigh it into half-gram and gram portions to be dissolved in 250 cc or 500 cc lots which leave less waste A catheter is placed in the bladder to empty it The bladder is then irrigated gently (without distention) with water, after which clorpactin is injected In patients with a very sensitive bladder only an ounce or two is instilled for a minute This is withdrawn, the bladder again irrigated with water, and 1 ounce of 2 per cent metycaine instilled in the bladder just before the catheter is withdrawn In less sensitive patients the bladder is dilated to comfortable capacity with clorpactin, which is then withdrawn Several such interchanges are used so that the solution is in contact with the bladder for 3 to 5 minutes We have also tried more forceful overdistention in the hospital on anesthetized patients but do not find that the results differ significantly We have followed the suggestion of O'Conor in repeating the treatments weekly for about

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[4] Zwerling, M Clorpactin WCS 90 A new antiseptic Arch Otolar, 62 157 1955

[5] Lattimer J K and Spirito A L Clorpactin for tuberculous cystitis J Urol 73 1015, 1955

5 treatments In the hospital we have repeated treatments as often as every 4 days After the initial course a month elapses following which another irrigation with clorpactin is given After that we have had the patient return at such intervals as she deems necessary

The first treatment or two is apt to be more distressing than instillation of 2 per cent $AgNO_3$ A few patients have required hot sitz baths and codeine afterward, but we have not had to make any house calls We have had no serious untoward effect or sensitivity Hematuria rarely ensues One patient had chills and fever after treatment All had temporary aggravation of symptoms for 12–48 hours

We have treated 20 patients by this method in the last 6 months Eighteen of these were women Four of the group were under 40, five between 40 and 60, eight between 60 and 80, one over 80 Fourteen were married, four were widows, one single and one divorced Eighteen had been previously treated by other methods, varying in time from 1 to 15 years Previous treatment had consisted of overdistention of the bladder with water, instillation of 2 per cent $AgNO$, urethral dilation, urinary antiseptics, light fulguration, ureterosigmoidostomy (in one case), and probanthine Fifteen patients had had from 1 to 14 previous hospitalizations for treatment, five had had none Ten had had previous operations, most of them pelvic Clorpactin has been used on each patient from 1 to 10 times, with an average total of five for each

Symptoms which required treatment were as follows frequency in all, nocturia in most, urethral and bladder pain in many, hematuria in 2 As one patient expressed herself, she went so often she met herself coming back Bladder capacity varied before treatment from 3 to 20 ounces Regardless of bladder capacity all complained of small voidings Other diseases we have found coincidentally in this group are multiple sclerosis, cholelithiasis, epilepsy, manic depression psychosis, diverticulosis, caruncle, carcinoma of the prostate, prostatic hypertrophy, urethral stenosis, hydronephrosis, granular urethritis, vaginitis and asthma

RESULTS

First let us dispose of the unsuccessful results Three were not improved, one doubtful and 1 only slightly One of the failures had previously had a ureterosigmoidostomy without relief from the operation or subsequent clorpactin Ultimate cystectomy was done Two of the failures were just not improved The slightly improved patient also had multiple sclerosis The doubtful patient also had carcinoma of the prostate and was improved by clorpactin and stilbestrol Two patients had been treated too recently to evaluate and 1 has not been followed

The remaining fourteen all report that subjectively they have been more relieved than by any previous method of treatment Bladder capacity has increased The ability to utilize the maximum bladder capacity has improved, thus lessening greatly the frequency and nocturia In all 14 urethral burning and pain in the bladder have become almost abolished. Hematuria has stopped. No patient has expressed any regret in the change to clorpactin. In no instance where the patient has been cystoscoped after completion of treatment have we been unable by overdistention of the bladder to demonstrate the area of interstitial cystitis so it does not cure. It does however ameliorate symptoms, make life more pleasant and give us something more effective to offer in the treatment of interstitial cystitis.

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RECONSTRUCTION OF URINARY BLADDER IN CHILDREN WITH EXSTROPHY

JOHN K LATTIMER, ARCHIE L DEAN, JR, CLEMENT FUREY AND LLOYD BALLANTYNE

From the Squier Urological Clinic and the Department of Plastic Surgery, Columbia University and Presbyterian Hospital, New York 32, N Y

In the treatment of exstrophy of the urinary bladder, Sweetser's modification of the Mikulicz operation for reimplanting the bladder into the abdomen has attracted great interest among both the physicians and parents of these unfortunate children Previous techniques for dealing with this condition, utilizing ureteroenterostomy in various modifications, have left a great deal to be desired For instance, in some children the anal sphincter was not competent to retain urine In others there was a prolapse of the rectum Strictures at the point of anastomosis between the ureter and the bowel were all too common Infection and acidosis were constantly in the offing We were therefore happy to try this new technique when Dr Sweetser demonstrated its feasibility

TECHNIQUE

Like Dr Sweetser, we free up bladder and urethra, infolding them into a sac and tube We free up a strand of muscle and fascia from the top edge of the pelvic diaphragm and wrap this strand around the new urethra at the bladder neck In males we transplant the urethra to the bottom of the penis The prepuce may be used as a tube to make the urethra reach the tip of the penis A suprapubic cystostomy tube is left in place for 2 weeks A suture through the perineum, to hold the bladder down, does not appear to be necessary It is certainly not desirable to free up the bladder too much, lest the blood supply be damaged, or the ureters kinked

The fascial defect is bridged by flaps of anterior rectus sheath and the skin closure is done in a series of Z plasties by the Department of Plastic Surgery

RESULTS

We have done seven of these operations and we have observed the results in 1 case done by Dr Ralph Yeaw and 5 cases done by Dr Sweetser Ten were males and three were females In ten the operative procedures have been completed None are continent, although they are all below the expected age for continence All can accumulate urine in the bladder and eject it, in addition to dribbling almost constantly Bladder capacities average 75 cc Four out of eight had urethral strictures which required dilatation Reflux is present in most of the ureters, but appears to be a feature of the exstrophic ureter rather than of this technique In those cases in the past in which the ureteral orifices were transplanted into the bowel, reflux has occurred in over half of our cases

Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass, June 4-6, 1957

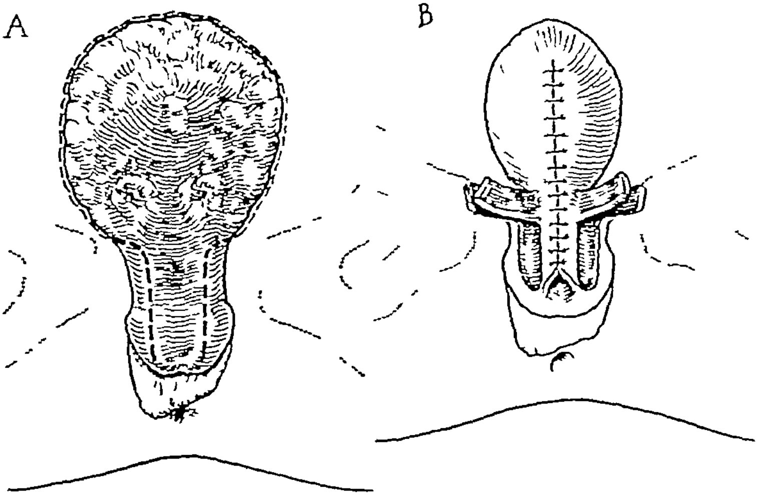

FIG 1 A, an incision is made around exstrophied bladder and along margins of open urethra This incision is deepened until all thicknesses of bladder wall and urethra can be freed from surrounding tissues sufficiently to form a sac and tube

B, after bladder and urethra have been formed a strand of muscle is liberated from top margin of the incomplete triangular ligament This strand of muscle is raised on each side so that two halves can be joined around urethra near bladder neck This muscular connection with pelvic diaphragm may provide some sphincteric action later

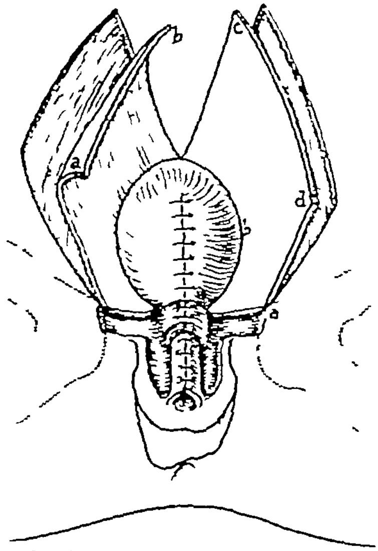

FIG 2 After bladder and sphincteric ring have been formed, flaps of anterior rectus sheath are raised on each side These flaps are used to cover bladder like two sides of double breasted coat Their lower margins are sutured to top of incomplete pelvic diaphragm and to margin of new sphincteric ring

OPTIMUM AGE

The optimum age for this operation appears to us to be somewhere in the vicinity of six months If one waits longer the bladder wall may become covered with thickened granulation tissue to the point where it can not be inverted to

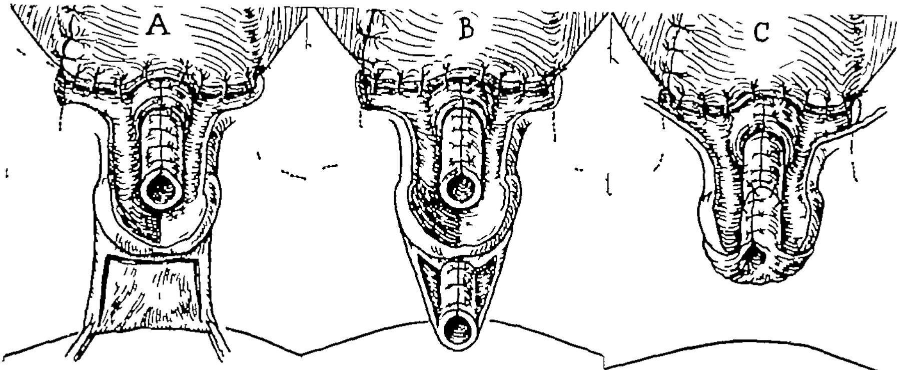

FIG 3 Flap of foreskin is liberated (*A*) and rolled into a tube (*B*) This is drawn into end of open penis and joined with incomplete urethra (*C*) This maneuver does away with strictures at meatus, and lessens incidence of pinhole fistulas along the dorsum of penis

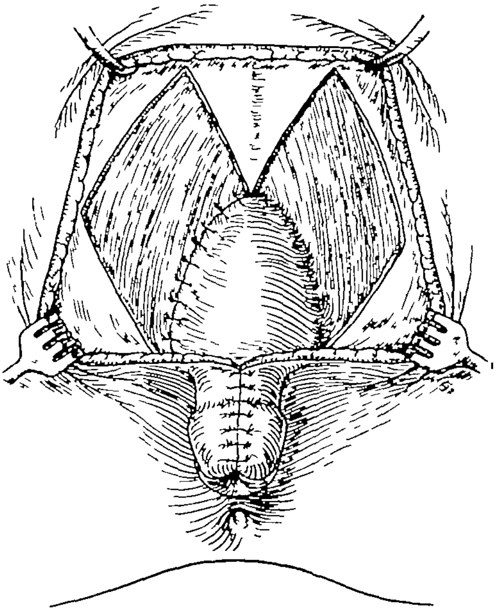

FIG 4 New urethra is transplanted to bottom of penis and subcutaneous tissues and skin are brought together above urethra Skin of abdomen is undermined by plastic surgical methods and brought together over midline in whatever design appears optimum for each case

make a reservoir of satisfactory size We have done this operation at various ages ranging from 3 months to 3 years and the younger children appear to have done better If the bladder is too small, either originally or as a result of granulations and contraction, we still attempt to roll it in upon itself In one patient, where the bladder was extremely small, the bladder size increased to satisfactory dimensions after the operation, but hydroureter developed This may have been due to stricture of the urethra rather than to the small bladder capacity Nevertheless, this appears to be a technical hazard If the bladder is large and flexible, there is less need to do the operation early

DISADVANTAGES OF TECHNIQUE

This is a formidable operative procedure from the point of view of operating time In most of our cases some eight hours were required for the operation, with the urologist working on the urinary tract for three or four hours and the plastic surgeons then coming in to work for three or four more hours to close the skin in a satisfactory fashion The length of time involved, with these tiny children, sometimes made it advisable to do the operation in stages, the bladder portion being done first, down to the creation of the sphincter, with the penile portion being done later, in the male children Strictures and pinhole fistulas along the dorsum of the new penis are a hazard, but since these are technical matters, they can be overcome with experience

The principal concern in regard to this operation is the uncertainty as to whether or not the sphincter mechanism will work Since none of our children has as yet reached an age when he or she might be actively interested in cooperating to achieve continence, it is impossible to estimate whether or not any will ever have satisfactory urinary control They are definitely below par for their age group at this time, but we have been so encouraged by the success of voluntary efforts on the part of patients with epispadias, to control their urine, that we have some hope that these children can achieve control in later life The possibility also exists that the continuing lateral growth of the child will pull open the newly-formed urethra, especially in the young female patients

ADVANTAGES OF TECHNIQUE

The advantages of this technique are considerable First of all it is a safe operation It is primarily superficial and there are no dangerous intraperitoneal points of union where urine might leak, as in the techniques employing ureteroenterostomy Secondly, we are not plagued with either acidosis or infection to any extent There is no increased opportunity for strictures of the ureters since there are no new anastomoses between the ureters and the bowel This technique more nearly duplicates Nature's own pattern for the design of the urinary tract This is most appealing to the parents of these children, who would a thousand times rather have an attempt at restoration in the direction of normalcy, rather than a transplantation of the ureters into the intestine Lastly, this technique is revocable Nothing has been lost and nothing has been destroyed by an attempt at this operation The ureters can still be transplanted into the intestine, into a segment of ileum or into the skin, as before, if this technique does not prove practical

We have had occasion to compare the effectiveness of the Coffey 1, the Leadbetter, the Maydl and the Goodwin techniques, with and without colostomy, in substantial series of cases It is our current view that this new technique is worthy of evaluation and that all children with exstrophy should have the benefit of at least one attempt to infold the bladder back into the abdomen, by this new method

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A SIMPLIFIED TECHNIQUE FOR CYSTECTOMY AND REPAIR OF THE ABDOMINAL DEFECT IN EXSTROPHY OF THE BLADDER

HARRY M SPENCE

From the Department of Urology of the Dallas Medical and Surgical Clinic and The University of Texas Southwestern Medical School, Dallas, Texas

Renewed efforts to close the exstrophic bladder and construct a sphincter mechanism in order to avoid the obvious shortcomings of ureterointestinal anastomosis in this condition are most commendable, and are yielding promising preliminary results The same may be said for the carefully thought out concept of Boyce and Vest in which a permanent colostomy is combined with anastomosis of the trigone to the isolated rectal pouch However, until such techniques are further perfected and their superiority proved by a substantial number of cases assessed in the light of long-term results, I believe that the current treatment of exstrophy should continue to be bilateral ureterosigmoidostomy, removal of the bladder, and correction of the associated external genital defects Indeed, experience in recent years with transplantation of the ureters to the sigmoid, carried out within the first year of life, has been quite acceptable and far superior to the results obtained in years past at a corresponding period of postoperative followup While no one can say that the results will continue satisfactory indefinitely, the trend to date warrants continuance until a proved better method is developed

The object of this paper, then, is to present the operative technique for removal of the bladder and repair of the abdominal wall defect after the ureters have been successfully transplanted to the bowel

In contrast to the multitude of articles dealing with the technique of ureterointestinal anastomosis, there is comparatively little in the literature regarding the technique of bladder removal in exstrophy Three different principles have been utilized 1) the development of flaps from the rectus fascia to cover the triangular defect in the lower abdominal wall after the entire bladder has been removed, 2) the use of tantalum mesh to bridge the defect again after removal of the entire bladder, and 3) removal of the bladder mucous membrane only with preservation of the fibromuscular wall and utilization thereof in closure of the defect The technique to be presented is of the latter type

Hutchins and Hutchins[1] in 1923 published a detailed description of the use of overlapping fascial flaps to close the defect This method is fairly satisfactory but involves extensive dissection, and on the few occasions where I have seen it used there has always been a certain amount of slough and slow healing Strong[2] (1950) presented a case in which he used tantalum mesh to bridge an extensive defect in an adult who had undergone several previous attempts at closure of the abdominal wall defect Postoperatively the result seemed excellent

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[1] Hutchins, E H and Hutchins, A F Exstrophy of bladder with successful transplantation of ureters into rectum Surg , Gynec & Obst , 36 731, 1923

[2] Strong, G H Repair of large abdominal defects following cystectomy for congenital vesical exstrophy A new technique J Urol , 64 743, 1950

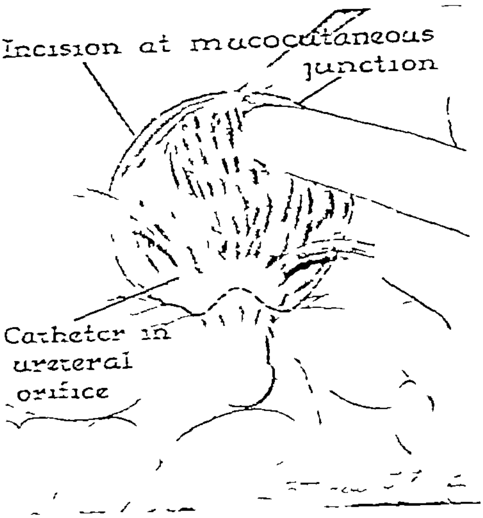
Incision at mucocutaneous junction
Catheter in ureteral orifice

FIG 1

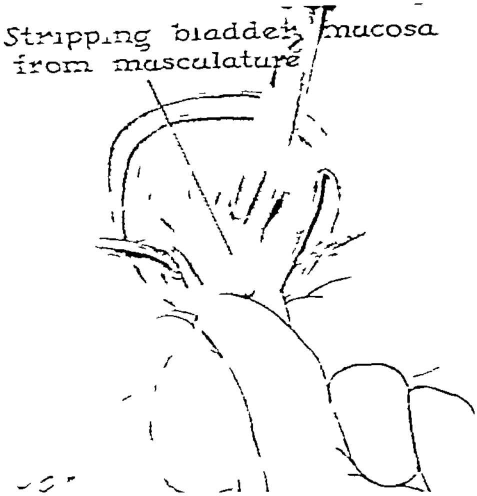

FIG 2

and undoubtedly such material may be necessary in an occasional case, particularly in the older age group However, it would be unnecessarily complicated if the same result can be obtained by a simpler measure In 1951 Hepburn[3] presented his method of reconstruction in which he removed the bladder mucous membrane with a sharp curette thereafter excising any excess fibromuscular bladder wall and suturing the cut edges The denuded operative surface was then closed over by drawing together the undermined skin margins after making lateral relaxing incisions which require skin grafting Gross[4] states that it is necessary only to remove the mucous membrane and tuck the bladder wall back

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[3] Hepburn T N Repair of exstrophy of the bladder J Urol 65 389 1951

[4] Gross P E Surgery of Infancy and Childhood Philadelphia W B Saunders Co, 1953 p 697

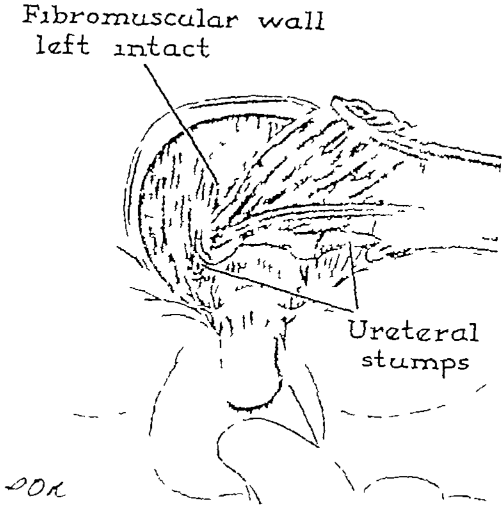

FIG 3

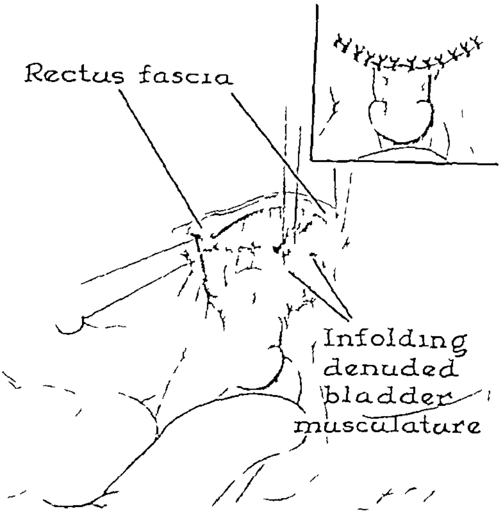

FIG 4

in the defect which is closed by drawing the rectus muscles and fascia together in the midline

The principle of the method to be presented is essentially that suggested by Hepburn, the differences being that 1) the bladder mucous membrane is dissected away by sharp dissection rather than relying on curettement and 2) the excess bladder wall is infolded for its additional tamponade effect rather than being excised The time at which this will be carried out depends on the smoothness of convalescence after the ureteral transplant and the general condition of the infant If all goes well the bladder may be removed about two weeks after the transplant but preferably six or eight weeks thereafter

The details of the procedure (figs 1–4) are as follows

1) After preparation of the surrounding skin bladder mucous membrane and external genitalia with pHisoderm, an incision is made with the scalpel about the entire circumference of the bladder wall at the mucocutaneous junction As this circumscribing incision approaches the bladder neck or rather the floor of the urethra care is taken particularly in the male to avoid damage to underlying prostate and ejaculatory ducts

2) The plane of cleavage between the bladder mucosa and the underlying fibromuscular structure is found and by blunt and sharp dissection the entire mucosa is stripped off and discarded Bleeding is controlled by gauze pressure except for arterial spurters which are tied Where the mucosa is adherent to the underlying tissue it is removed by sharp dissection One need not be overly meticulous as the objective is simply to remove all mucosa and leave the bulk of the bladder wall behind As the dissection approaches the ureteral orifices, each blind ureteral stump is removed intact

3) The denuded bladder wall is next inverted by progressive rows of chromic catgut sutures which infold the tissues and serve to plug the defect between the diverging lower recti These rows of sutures are taken transversely and one is surprised to note how the upper fascial rim of the defect is drawn downward forming an additional closure layer

4) The skin is closed transversely after minimal undermining of its margins In several cases I have closed the skin under moderate tension with subsequent cutting out of the stitches but any raw surface has epithelialized with surprising rapidity and skin grafts have not been necessary

5) In the male the upper chordee of the epispadiac penis is corrected at this stage in similar fashion to the correction of the downward chordee in the hypospadiac penis by the Nesbit buttonhole technique (to be the subject of a later communication)

The technique has been used in 14 cases (9 male and 5 female patients) The resulting abdominal wall has been strong and solid in all, and the cosmetic result has been quite satisfactory

SUMMARY

A simplified technique for cystectomy and closure of the abdominal defect in exstrophy of the bladder is presented The essentials of the operation are removal of the mucosa and utilization of the infolded bladder musculature to aid in reconstructing the abdominal wall

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VALUE OF CYSTECTOMY IN MANAGEMENT OF CARCINOMA OF BLADDER

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The value of simple cystectomy in the treatment of carcinoma of the bladder is highly controversial At present, the majority of urologists throughout the country favor other methods of treatment Although the total number of cases included in our series of total cystectomy for carcinoma is comparatively small, an analysis of our 5-year results leads to some interesting conclusions

A total 48 cases, all operated upon prior to March 1, 1951, is presented Simple cystectomy with ureterosigmoidostomy, usually performed in one stage, was performed in all except one patient In this case, a diverting colostomy was performed at the time of surgery and the ureters transplanted into a rectal pouch There were two operative deaths (4 2 per cent) Thirty patients died within the 5-year period and 16 survived five or more years, a 5-year survival rate of 33⅓ per cent This figure compares favorably with that given for other methods of treatment Furthermore, included in the series were many cases with far advanced carcinoma, undertaken early in our experience, in which surgery was performed with the full realization that the possibility of cure was almost negligible

Carcinoma was the cause of death in 17 patients Other causes are listed in table 1 Of significance in this group is the fact that renal failure was the direct cause of death in only three Of these, one had extensive renal damage with marked bilateral hydronephrosis and hydroureter previous to surgery Although he had remarkably poor renal reserve, he survived the extensive surgery unusually well, experienced considerable improvement in renal function, and lived a normal active existence for a period of about 18 months However, he suffered a marked acidosis throughout that entire time requiring large doses of sodium bicarbonate He was not too co-operative and died presumably of acidosis while visiting in another state As is noted, the other causes of death cover those diseases that one would anticipate in the age group from which these patients were taken

Of those who died, the average survival was 18 1 months Excellent palliation was obtained in almost every instance and we believe that the procedure was fully justified for that reason alone even though it was not curative Practically all of the cases were graded according to Jewett's classification (table 2) As was anticipated, of those who died 67 6 per cent fell in the class B and C group However, surprisingly enough 62 5 per cent of the survivor group also fell into this classification, proving that even fairly far advanced carcinoma is occasionally amenable to radical removal The comparatively small number of cases in the

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TABLE 1

Renal failure	3
Coronary thrombosis	2
Cerebral thrombosis	1
Hypertensive cardiovascular disease	1
Pneumonia	1
Osteomyelitis of the cervical spine	1
General debility	1
Unknown	3

TABLE 2 *Jewett classification*

	A	B	C	Unclassified
Alive	37 5	37 5	25 0	
Dead	16 72	20 0	47 6	16 6

Values are expressed in per cent

TABLE 3 *Grade and type of tumor*

	Epidermoid	Transitional Cell			
		I	II	III	IV
Alive	6 3	6 3	37 5	43 6	6 3
Dead	16 7	3 3	30 0	33 3	16 7

Values are expressed in per cent

Jewett classification A is due to the fact that only those cases with demonstrable muscle invasion or with a Broders' classification of group 2 or above were treated by cystectomy

Table 3 shows the survival rate according to the grade of tumor Of note is the fact that 50 per cent of the survivors are in the grade 3 and 4 classification Also the one case of epidermoid carcinoma is a 5-year survivor From tables 2 and 3 it is apparent that a very respectable 5-year survival rate has been obtained in spite of the fact that in practically all cases a fairly high degree of malignancy and bladder penetration was present

The essential facts concerning the 5-year survivors are presented in table 4 None of the patients in this group have clinical evidence of carcinoma at the present time

A study of the renal status as obtained from excretory urography and blood chemistry findings was obtained on every patient in this group four and a half or more years after surgery One patient underwent nephrectomy prior to cystectomy and therefore, there were only 31 renal units available for study Of these, 22 or 70 9 per cent are considered to be normal having no evidence of or at most a grade 1 hydronephrosis Of the remaining patients, in only 3 cases is the overall renal status considered as poor

The point has been frequently made that although patients may survive cystectomy and urinary diversion, many of them are essentially renal cripples and are unable to carry on their usual normal activities Therefore, we have made a special effort to determine the amount of physical activity which these patients can perform and find that only two of the group are unable to carry out normal activities and a third is *partially disabled Renal sepsis has been present in five* of the surviving sixteen but in every instance it has been readily controlled by suitable antibiotic therapy, and at no time has it interfered to any significant extent with the patient's ability to carry on normal activities

One of the patients has required reimplantation of ureters into an isolated ileal segment because of progressive hydronephrosis and renal deterioration

TABLE 4

Name	RT K	LT K	Died	Overall Renal Status	Jewett	Grade Tumor	NPN	CO	Sepsis	Normal Activities
E H	Normal	Normal		Excellent	B	2	25	25	0	Yes
G F	No shadow non-function pre op	Normal	7 yrs	Good	B	1	25 85*	16– 27 7	0	Yes
E B	No shadow	No shadow		Poor	A	2	48	14 2	+	No
R P	Normal	Normal		Good	A	2	57 5	18	0	Yes
C H	No kidney at cystectomy	Normal		Fair	B	2	30 5	14 3	+–	No
F G	Normal	Normal		Excellent	A–B	2	20	23 5	+–	Yes
H C	Grade 1	Normal		Good	B	3	29	28 6	+	Yes
A L	Grade 2	Grade 2 with stag horn calculus		Poor	A	3	34	15	0	Partially
M L	Normal	Normal		Fair	A	2	39	16 3	0	Yes
J S	Grade 2 Poor function	Normal config Poor function	5 yrs	Poor	C	Epidermoid 4	32	19	+	No
A F	Grade 1	Grade 1	5 yrs	Good	C	3	26	26 8	0	Yes
A K	Normal	Normal		Good	C	Epidermoid	17 5	20 5	0	Yes
M T	Grade 2	Grade 1		Excellent	A	3	31	18	0	Yes
J K	Grade 1	Normal		Excellent	C	3			0	Yes
G K †	Normal	Normal		Excellent	A	3	20		0	Yes
L L ‡	Grade 2	Normal		Good	B	3	20	25 9	0	Yes

* Terminal

† Urinary diversion to isolated rectal pouch

‡ Ureterosigmoidostomy Converted to ileal loop after 3½ years because of renal deterioration

This process was progressing although the patient was carrying on normal activities and considerable persuasion was required to convince him of the necessity of additional surgery An excellent result has been obtained with the ileal segment one kidney and ureter have returned to normal pyelographically the other still maintains about a grade 2 dilatation and the blood nonprotein nitrogen and CO_2 combining power have been completely normal since the ileal diversion I believe that this particular case emphasizes the importance of regular periodic observation of all patients with urinary diversion irrespective of type Furthermore I believe that to some extent it demonstrates the superiority of the isolated ileal segment as a means of urinary diversion

An autopsy was obtained on all three of those patients who survived more than 5 years and died subsequently Several lessons have been obtained from these postmortem examinations and a brief evaluation of each is in order

G.F survived for 7 years During his sixth year marked hypertension with a pronounced azotemia developed Up until that time he was performing regular activities as a day laborer and actually continued to do so until within about one month of his death He had had a nonfunctioning atrophic kidney on the right prior to the original surgery and it never became functional however the left pyeloureterogram was normal in every respect on repeated examinations as long as 6 years postoperatively When the nonprotein nitrogen rose it was believed that the elevation was secondary to malignant hypertension However at autopsy the patient was found to have numerous calculi with a definite hydronephrosis in the kidney which pyelographically had remained normal for a 6-year period Since there was no evidence of pelvic dilatation or calculi approximately 9 months before death I believe it is possible that the production of calculi occurred as a terminal event but they undoubtedly contributed to the fatal outcome This patient originally had extensive recurrent grade 1 papillomatosis of the bladder There was no evidence of carcinoma at autopsy

J S survived for 5 years and died of multiple cortical abscesses of both kidneys During the entire period of his survival he had shown a grade 2 hydronephrosis on the right and a normal configuration on the left with bilateral poor function on excretory urography His renal status was always listed as poor This patient resisted all persuasions that he submit to diversion of the colon above the ureterosigmoidostomy or any other type of urinary diversion The character of his lesion was recognized and had he been more co-operative a more favorable result might have been obtained Although he had an epidermoid carcinoma grade 4 with penetration through the entire bladder wall careful search for carcinoma at autopsy revealed no signs of residual tumor This case again re-emphasizes the fact that every patient with bladder carcinoma should be given a chance at cure by radical means even though the lesion appears to be far advanced If there are no demonstrable lymph node metastases and the bladder is not fixed laterally cystectomy should be done

A.F had chronic lymphatic leukemia which was under fair control In addition he had a grade 3 carcinoma with penetration through the entire bladder wall for which cystectomy and ureterosigmoidostomy were performed Con-

valescence was uneventful and although the ureters showed a mild, grade 1 dilatation bilaterally and his overall renal status was listed only as good, he enjoyed excellent health as far as the kidneys were concerned Thrombophlebitis eventually developed and the patient died of pulmonary embolus At autopsy the upper urinary tract was found to be in good condition There was minimal ureteral dilatation and the ureterosigmoidostomies were open and functioning well There was no evidence of carcinoma anywhere in the pelvis However, a single solitary nodule about the size of a hickory nut was found in the liver which, on microscopic section, was found to be transitional cell carcinoma This disconcerting feature emphasizes a fact with which we are all familiar, namely, that although there may be no clinical evidence of carcinoma, some of our survivors may be harboring occult metastatic carcinoma at the present time and a 5-year survival certainly does not mean that there is a cancer cure

SUMMARY

A closed series of 48 cases in which cystectomy and ureterosigmoidostomy have been done for carcinoma of the urinary bladder is presented There are 16 five-year survivors, a 33⅓ per cent survival rate

Overall renal status in this group has been acceptable

Of the group of survivors, all but three have been able to carry on normal duties In my opinion cystectomy for carcinoma of the urinary bladder still has a significant place in the management of that highly lethal disease

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URETERAL SUBSTITUTION BY ISOLATED ILEAL LOOP: ILEOURETEROPLASTY AND ILEOPYELOPLASTY

S. A. MacDONALD AND P. N. KATARIA

From the Montreal General Hospital and Department of Surgery, McGill University, Montreal, Canada

Clinical experience with the grafting of isolated small bowel segments to the urinary tract is still limited. There has been a long delay in accepting such procedures which were first suggested in 1888. In that year Tizzoni and Foggi[1] replaced the bladder in a dog with an isolated small bowel loop anastomosed to the proximal urethra. A few years later in 1894 Fenger[2] discussed the possibility of replacement of the ureter with small intestine; apparently he never executed his suggestion. A very long delay occurred before Fenger's idea of replacing the ureter was applied clinically. Bitker[3] in reviewing the literature on this subject found only 3 clinical reports of ileoureteroplasty prior to 1950 and a total of 17 until 1953. Since then various authors[4-9] have published 19 additional cases, bringing the present total number to 36. Two additional cases are embodied in this report. In one of them an ileopyeloplasty was done. Such an operation is reported in only four of the previously published cases.

The histories of the 2 patients reported here are given in some detail because they illustrate so clearly the dangers of prolonged ureteral catheter drainage. Likewise, the operative reports are detailed because of the lack of precise information of the technique employed in most of the published reports.

CASE REPORTS

Case 1. Ileoureteroplasty. A. M., aged 48, was first seen in 1947 when cystoscopy revealed a flat solitary tumor involving the posterior wall and fundus of the bladder. A partial cystectomy was done. Eight months later two small lesions were excised transurethrally from the floor of the bladder neck, an area remote from the original growth.

Unfortunately no further examination was possible until 7 years later when in 1954 the patient re-appeared with a large flat tumor involving the entire upper half of the internal orifice of the bladder and the adjacent superior wall

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Read at annual meeting of American Association of Genito-Urinary Surgeons, Osterville, Mass., June 4-6, 1956.

[1] Tizzoni, G. and Foggi, E.: Die Wiederherstellung der Harnblase. Centralbl. f. Chir., 15: 921, 1888. (See Melnikoff, A. E.: Sur le remplacement de l'urètere par une anse isolee de l'intestin grele. Rev. Clin. Urol., 1: 601, 1918.)

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in the so-called blind area Cystoscopically this tumor appeared much more malignant than the original lesion Transurethral biopsy confirmed the clinical impression of a more anaplastic tumor superficially invading the bladder wall

Total cystectomy, prostatectomy, and seminal vesiculectomy were accomplished in July 1954 The ureters were brought to the skin of the anterior abdominal wall In the immediate postoperative period the distal portion of the left ureter sloughed, requiring excision and reimplantation in the abdominal wall A good external rosette was obtained, and the patient was discharged from the hospital wearing a Singer cup Since that time, 2 years ago, no further difficulty has been encountered on that side, and that kidney remains apparently normal

On the right an adequate external nipple of ureter was not obtained, and an indwelling catheter was necessary All the usual complications associated with this type of drainage resulted Within 4 weeks, the first of many episodes of acute pyelonephritis occurred For several months leakage of urine from the skin stoma about the catheter was a source of annoyance Increasing difficulty began to be encountered in changing the catheter Finally, 5 months after cystectomy, this became impossible The fibrosed and stenosed distal portion of the ureter was excised, and a new cutaneous ureterostomy was made in December 1954 Continued use of a catheter was necessary, and the patient was almost constantly disabled by pain and pyelonephritis

Repeated x-rays showed increasing pyelonephritic destruction of the right kidney (fig 1, *A*) and 8 months after cystectomy the urinary output from the kidney began to decrease Finally, 15 months after the bladder excision in October 1955, operative interference seemed imperative in order to preserve the remaining renal function At that time, even though the left kidney was normal, it was not thought advisable to remove the damaged right kidney It seemed obvious that what was required was a new ureter which would not require an indwelling catheter

Operation (October 25, 1955) A long right paramedian incision was made The small bowel was displaced into the left side of the abdominal cavity An incision was made longitudinally through the peritoneum overlying the ureter which could be felt as a laterally placed tight band, extending from the posterior abdomen to the anterior abdominal wall This peritoneal incision deviated superiorly and inferiorly, lateral to, and parallel with the cecum and ascending colon Inferiorly it extended to the cecal tip, superiorly to the upper margin of the transverse colon The cecum, ascending colon, and hepatic flexure were reflected medially without difficulty The ureter was then dissected free from the posterior abdominal wall The distal portion was densely fibrosed and grossly thickened This change extended almost to the lower pole of the kidney where the ureter became relatively normal and easily intubated Immediately below this area a definite stricture could be identified

The kidney itself was high and tightly embedded in fibrous tissue It could not be well defined by palpation It was thought that if an anastomosis to the renal pelvis were necessary, this anterior approach would not be satisfactory or

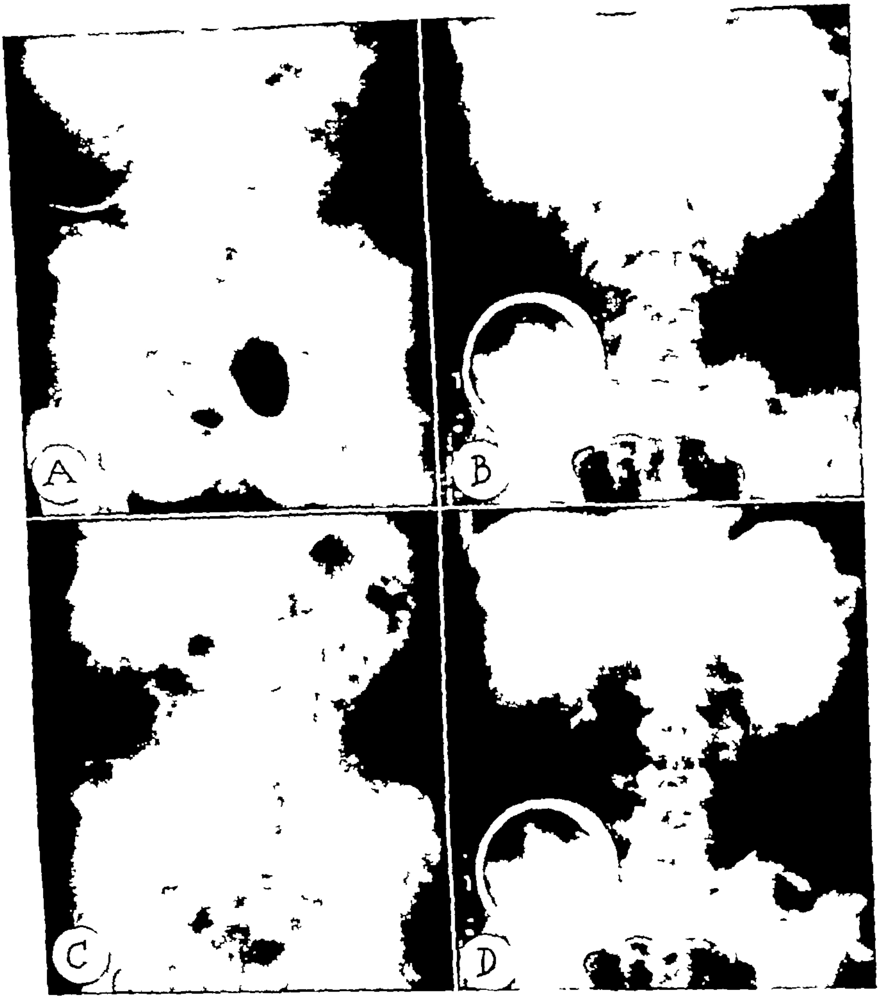


FIG 1 Case 1 A, retrograde right pyelogram Extensive pyelonephritic damage after 7 months of catheter drainage Further destruction occurred prior to ileoureteroplasty 8 months later B, 2 weeks after ileoureteroplasty Excellent function (5 minute film), calyceal pattern already returning to more normal appearance C 8 weeks after ileoureteroplasty Note relatively normal left upper urinary tract after 20 months of successful "cup" drainage D note remarkable improvement in right kidney 8 weeks after ileoureteroplasty (15 minute film)

adequate The accuracy of this observation was proven by the findings in our second patient

Inspection of the ureter showed that division at about the lower pole of the kidney would be satisfactory (fig 2, A) Attention was then directed to the formation of a small bowel loop The ileum was divided 6 inches from the ileocecal valve and again 12 inches proximal to that point In order to obtain adequate mobilization it was necessary to divide the mesentery almost to its base at both ends of the loop Great care must be exercised in this portion of the

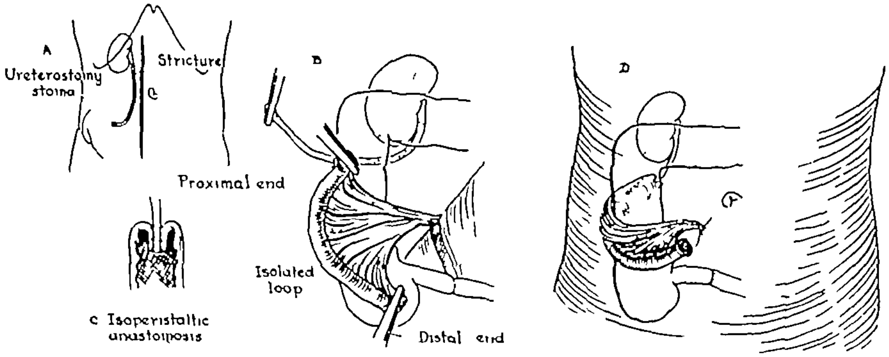


Fig 2 Case 1 *A*, loop brought anterior to both large and small bowel Ureter later severed just below transverse colon *B*, anastomosis completed Relationship of colon, loop and ureteral stump

dissection lest a major vessel of supply to the required loop be divided inadvertently This is best prevented by first carefully inspecting the vascular pattern, and then dividing separately, over the opened blades of a blunt instrument, the two peritoneal layers enclosing the vessels and fat of the mesentery As the mesenteric division proceeds, the proximal end of the loop can be brought repeatedly, if necessary, to the anastomotic site to determine whether sufficient mobility has been obtained When the loop was sufficiently mobilized, an end to-end anastomosis of the ileum was done beneath the ileal loop (fig 2, *B*) The mesenteric defect was then closed with interrupted sutures The loop with its attached vascular pedicle then lay on top of the reformed mesentery

The best fit with the ureteral stump seemed to be achieved by bringing the loop around the lateral aspect of the hepatic flexure to the ureter The apposition thus obtained appeared to be more satisfactory than that which would have resulted from the insertion of the loop through the mesentery of the flexure When the course of the new channel had thus been determined, the dilated proximal ureter was divided obliquely and anastomosed directly to the proximal end of the ileal loop behind the hepatic flexure Interrupted through and through sutures were used as a first layer inverting both ureteral and bowel walls A mucosal-to-mucosal junction was thereby effected Two additional layers of interrupted sutures were placed through the bowel serosa and adventitia of ureter These two layers of sutures inverted the end of the loop with its attached ureter An internal nipple of the ureter with the attached inverted bowel wall was thus produced The ileal loop was brought around the lateral side of the ascending colon, thence along its anterior surface Internal herniation was prevented by suturing the loop and its mesentery to the underlying large bowel and adjacent peritoneum (fig 2, *C*, *D*)

The colon was then secured in its normal position by approximating the divided margins of the posterior peritoneum

The distal end of the loop was brought forward directly to the abdominal wall, and a cruciate incision was made in the fascia to diminish the possibility of future stenosis Several stitches approximated the bowel serosa and peritoneum Finally the protruding nipple of bowel was everted and stitched to the skin

Postoperatively, no difficulties were encountered A Foley catheter was left in the loop for 4 days, after which a Singer cup was cemented over the stoma

The preoperative lumbar pain was relieved completely, and the patient's toxicity disappeared His general condition rapidly improved in every way Most pleasing was the rather startling improvement in the functional capacity and pyelographic appearance of the right kidney (fig 1, *B*, *C*, *D*) At this time, 8 months after his operation, he seems to be completely rehabilitated

Case 2 Ileopyeloplasty Mr R M was seen at the age of 44 because of symptoms suggesting bladder infection The bladder mucosa was found to be thickened and coarsely edematous in an extensive area involving the trigone and the entire bladder neck The cystoscopic appearance suggested an inflammatory lesion and biopsy was negative for tumor Treatment of the existing infection produced no relief

Nine months later a second cystoscopy revealed mucosal changes of the same type, but more severe in character Biopsy revealed a transitional cell epithelial carcinoma with superficial invasion

Intracavity radiation was administered from a central radium source The calculated administered surface dose at the bladder outlet was 5,800 r, with 4,400 r at a depth of 3 cm The dose to the bladder vault was calculated at 5,000 r in an overall time of 5 days

Five months later the bladder capacity was 375 cc On this occasion cystoscopy revealed a marked improvement in the appearance of the mucosa in the trigonal region Again no actual tumor mass could be seen anywhere in the bladder In large areas, however, the previous changes were observed Both sides of the bladder neck and the entire right bladder wall were involved in a coarsely edematous, granular change, characteristic of infiltrating neoplasm Biopsy of these areas revealed tumor of the type previously observed

Because of the diffuse nature of the cancer and the widespread instability of the bladder mucosa, a total cystectomy seemed advisable This was accomplished October 14, 1953, one year after the original cystoscopy The bladder, prostate, seminal vesicles, and all pelvic lymph tissue were excised The ureters were transplanted to the skin The excised specimen showed only superficial invasion of the bladder wall and intramural lymphatics The obturator and all pelvic lymph nodes were negative for tumor

Many attempts were made to utilize Singer cups, but inevitably leaks developed, and unfortunately the patient was discharged wearing indwelling catheters on both sides During the next month there was constant low grade fever with occasional exacerbations Slight discomfort was present frequently in the left renal area

One month after leaving the hospital, the patient was readmitted with acute left pyelonephritis, and a blocked left catheter Reinsertion of a catheter on that side was not possible, and due to the existence of definite ureteral obstruction, exploration was necessary The distal ureter was found to be densely fibrosed and narrowed This terminal portion, about 3 inches in length, was excised and a new cutaneous stoma constructed

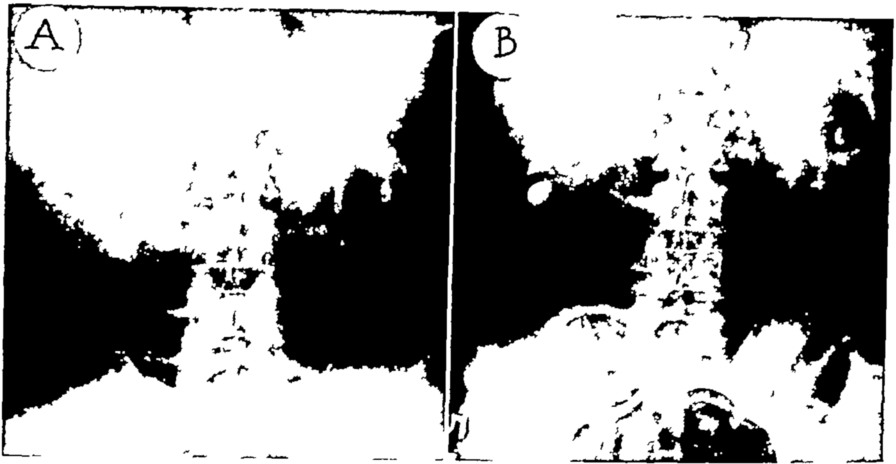


FIG 3 Case 2 *A*, 3-hour excretory urogram showing condition of right kidney after 28 months of ureteral catheter drainage No visible concentration of dye until 30 minutes after injection of dye *B*, 3 months after ileopyeloplasty Good concentration of dye (5 minute film) Marked improvement in calyceal pattern

The ensuing year was relatively uneventful, until its very end, when bilateral pyelonephritis appeared The infection was particularly violent on the right side A dense mass became palpable in the renal area, it was thought that pyemic abscesses of the kidney and perinephritis had developed A hectic fever persisted nearly 2 weeks A mixed infection was found in both kidneys, but Pseudomonas aeruginosa was the dominant organism After several drugs had been given without effect, polymixin eventually controlled the infection During this illness some diminution in the function of the right kidney became apparent

In the second post-cystectomy year two hospital admissions were necessary for pyelonephritis in the right kidney (fig 3, *A*) On several occasions difficulty was experienced in replacing one or the other catheter Finally at the end of the 2 years in December 1955, neither catheter could be inserted Fortunately, there was an adequate mucosal outpouching on the left A Singer cup was applied with greater success than previously, and has been worn since then without difficulty

On the right side, without a catheter over a 4-week period, from December 15, 1955 to January 14, 1956, the urinary output rapidly decreased, due to stenosing ureteritis After repeated efforts a filiform bougie was passed, and a catheter was inserted to the renal pelvis With adequate drainage the kidney quickly regained its functional capacity

The problems at this time seemed similar to those of the previous patient, first, the necessity for preserving the kidney, and, secondly, of providing a good functional ureter which would not require permanent intubation

Operation (January 24, 1956) See figures 4 and 5 A midline incision was made The small bowel was packed off in the left side of the abdomen The thick rigid tube of ureter was readily identified coursing up to the anterior abdominal wall

The appendix was adherent to the lateral abdominal wall, and would have interfered with mobilization of the cecum A routine appendectomy was done

The cecum, ascending colon, and hepatic flexure were mobilized and displaced medially Access to the ureter was thus obtained It was divided just beneath the anterior abdominal wall and mobilized by sharp dissection When several inches had been freed, catheterization was attempted Impassable obstruction was encountered at what was thought to be the ureteropelvic junction The ureteral dissection was carried as high as possible, but the renal hilum could not be visualized The kidney was high and densely incorporated in a mass of scar tissue It was decided that it would not be possible by means of an anterior approach to bring an ileal loop to the renal pelvis (fig 4, A)

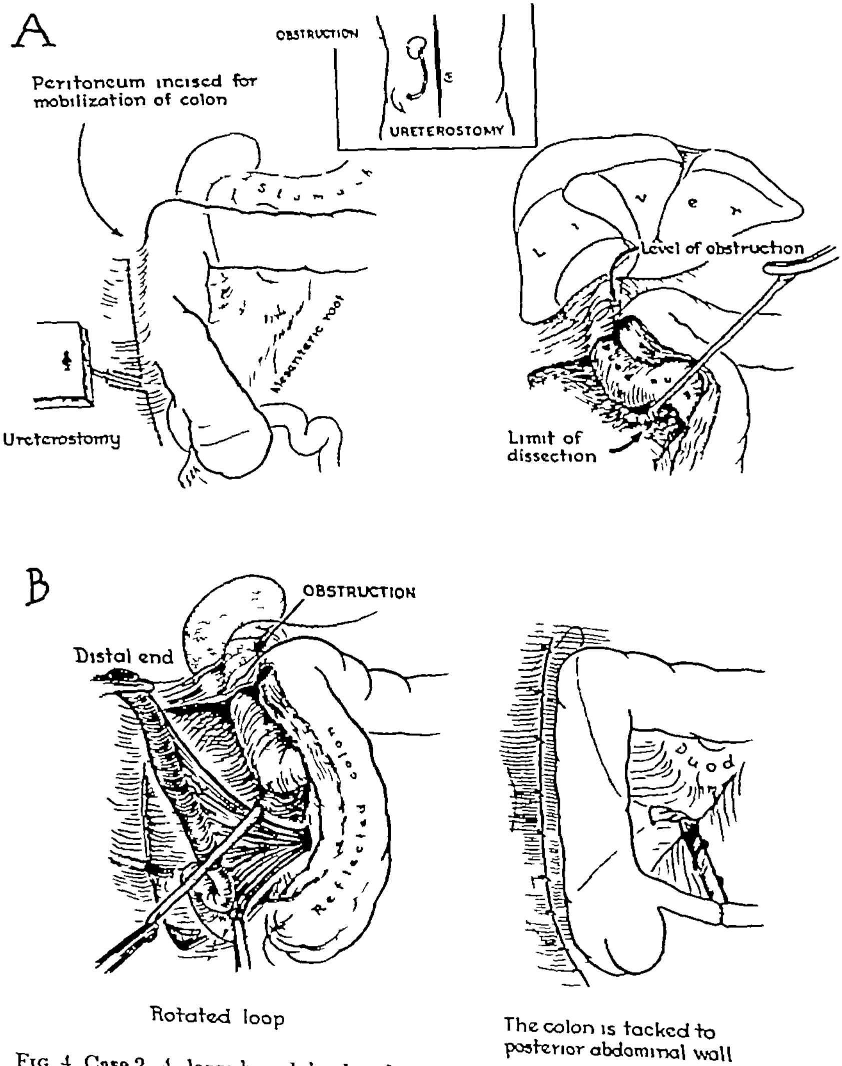
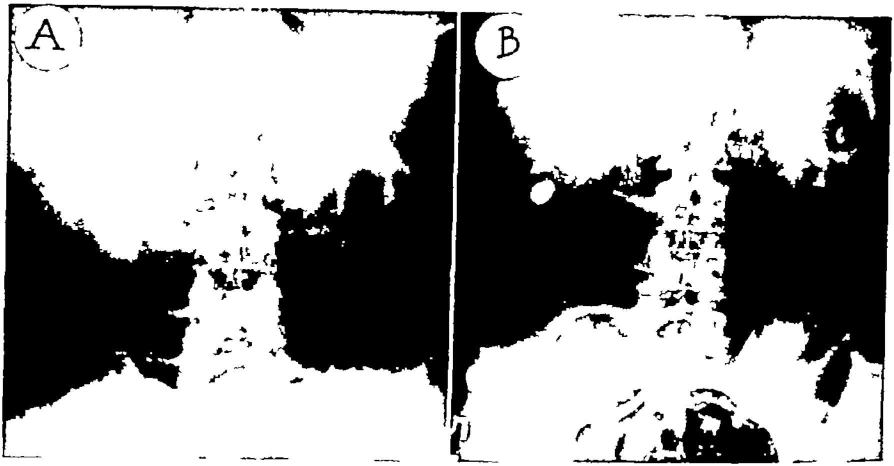


FIG 4 Case 2 *A*, large bowel displaced and duodenum partially freed Renal hilum still well above area of dissection *B* loop fully mobilized and passed through mesentery of ascending colon Right drawing shows loop in its new retroperitoneal position



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The cecum, ascending colon, and hepatic flexure were mobilized and displaced his general condition has improved markedly (fig 3, *B*) No episodes of fever, so common in the past, have occurred, and he has resumed his professional work There seems no reason why future difficulties should be encountered A Singer cup has been worn successfully over the ileal stoma ever since the operation

DISCUSSION

The provision of adequate drainage and the removal of the infection-producing catheters have had a profound effect on both these patients Their general health has improved so markedly that they have resumed their former occupations

During the early postoperative period, for approximately three weeks, almost daily removal of the cups was necessary in order to evacuate mucus With the passage of time its production has seemed to diminish, and at present the cups are being changed every 4 to 5 days If they are left in place too long, calcareous debris will collect on the skin, and may give rise to dermatitis

In only 4 of the 33 reported ileoureterostomies has the bowel loop been anastomosed to the renal pelvis Two of these were reported by Baum,[4] one by Moore,[5] and one by Rack [6]

In Baum's patients the left ureter was replaced The ileal loop was passed around the lateral aspect of the colon in one patient, and through the mesocolon in the other Access to the left renal pelvis probably is easier than to the right

Both Moore and Rack replaced the right ureter In Moore's patient the kidney seems to have been low, with an elongated extrarenal pelvis The anastomosis was done at a relatively low level inferior to the hepatic flexure Rack anastomosed an ileal loop to the pelvis of a solitary kidney The patient had worn a nephrostomy tube 2½ years As with our patient, who wore a ureteral catheter, recurrent attacks of pyelonephritis produced progressive renal damage and increasing azotemia Rack's report does not include operative details, but the anastomosis was effected through an anterior abdominal incision

In both our patients the possibility of placing the opposite ureter in the small bowel loop was considered seriously It was not thought wise to effect this change, because of the satisfactory drainage and the integrity of the contralateral kidney in both patients Furthermore, neither patient desired interference with what was considered an existing satisfactory solution of the problem, and neither one believed that the care of a second cup would add materially to the burden The further course of each patient has demonstrated the wisdom of each one's choice

CONCLUSION

Experience with these 2 patients and a review of those previously reported indicates that ileal replacement for part, or all of the ureter is a feasible and entirely satisfactory procedure

1414 Drummond St , Montreal 25, Canada

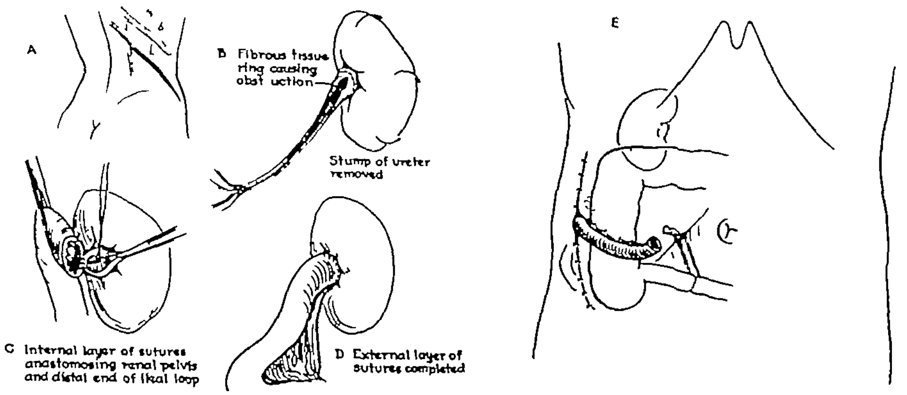
A
B Fibrous tissue ring causing obstruction
Stump of ureter removed
C Internal layer of sutures anastomosing renal pelvis and distal end of ileal loop
D External layer of sutures completed
E

FIG 5 Case 2 *A*, posterior dissection showing method of anastomosis *B*, antiperistaltic anastomosis completed Proximal end of loop sutured to renal pelvis, distal end opening on skin

A 10-inch loop of distal ileum was isolated The loop with its intact blood supply was passed through the mesentery of the ascending colon, and placed retroperitoneally in the right abdominal gutter At this time, one end of the loop should have been brought to its final position in the anterior abdominal wall, instead, the abdomen was closed with the entire loop beneath the posterior peritoneum (fig 4, *B*)

The patient was then placed on his left side and the kidney exposed through the bed of the twelfth rib The kidney was mobilized with difficulty by sharp dissection, which was necessary due to the marked fibrous perinephritis The ureter was divided longitudinally, and almost complete occlusion was found at the hilum of the kidney, the pelvis itself being entirely intrarenal

The posterior rim of the renal hilum was retracted and an opening 1 inch long was made in the pelvis The ileal loop approximated this opening more easily when rotated A No 20 Foley 5 cc catheter was passed along the loop into the renal pelvis Then an antiperistaltic anastomosis was made A mucosal-to-mucosal union was effected with interrupted sutures of No 000 chromic cat gut These were reinforced with a second external layer (fig 5, *A*, *B*, *C*, *D*)

The posterior portion of the incision was then closed and the patient rotated to a partially supine position The proximal portion of the ileal loop was then brought through the posterior peritoneal layer lateral to the cecum, to the anterior abdominal wall The manipulation of the loop within the abdominal cavity was a blind procedure and should have been done at an earlier stage (fig 5, *E*)

The first few days after operation were associated with an expected adynamic ileus However, adequate bowel motility did not return and there was persistent moderate painless distension This had not been relieved by the tenth postoperative day A superadded mechanical factor in the obstruction was suspected and the abdominal wound was reopened Two softly adherent loops of small bowel were found in the true pelvis They were separated by finger dissection, and an enterostomy was done above the obstructed area

The patient's further convalescence was uneventful In the subsequent months his general condition has improved markedly (fig 3, *B*) No episodes of fever, so common in the past, have occurred, and he has resumed his professional work There seems no reason why future difficulties should be encountered A Singer cup has been worn successfully over the ileal stoma ever since the operation

DISCUSSION

The provision of adequate drainage and the removal of the infection-producing catheters have had a profound effect on both these patients Their general health has improved so markedly that they have resumed their former occupations

During the early postoperative period, for approximately three weeks, almost daily removal of the cups was necessary in order to evacuate mucus With the passage of time its production has seemed to diminish, and at present the cups are being changed every 4 to 5 days If they are left in place too long, calcareous debris will collect on the skin, and may give rise to dermatitis

In only 4 of the 33 reported ileoureterostomies has the bowel loop been anastomosed to the renal pelvis Two of these were reported by Baum,[4] one by Moore,[5] and one by Rack [6]

In Baum's patients the left ureter was replaced The ileal loop was passed around the lateral aspect of the colon in one patient, and through the mesocolon in the other Access to the left renal pelvis probably is easier than to the right

Both Moore and Rack replaced the right ureter In Moore's patient the kidney seems to have been low, with an elongated extrarenal pelvis The anastomosis was done at a relatively low level inferior to the hepatic flexure Rack anastomosed an ileal loop to the pelvis of a solitary kidney The patient had worn a nephrostomy tube 2½ years As with our patient, who wore a ureteral catheter, recurrent attacks of pyelonephritis produced progressive renal damage and increasing azotemia Rack's report does not include operative details, but the anastomosis was effected through an anterior abdominal incision

In both our patients the possibility of placing the opposite ureter in the small bowel loop was considered seriously It was not thought wise to effect this change, because of the satisfactory drainage and the integrity of the contralateral kidney in both patients Furthermore, neither patient desired interference with what was considered an existing satisfactory solution of the problem, and neither one believed that the care of a second cup would add materially to the burden The further course of each patient has demonstrated the wisdom of each one's choice

CONCLUSION

Experience with these 2 patients and a review of those previously reported indicates that ileal replacement for part, or all of the ureter is a feasible and entirely satisfactory procedure

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EXPERIENCES WITH THE JOHANSEN-DENIS BROWNE TECHNIQUE OF URETHROPLASTY

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For 2 years the Johansen technique for urethroplasty has been utilized in selected cases of strictures of the male urethra at University Hospitals The purpose of this report is to evaluate the results of this operative procedure

During the 2 years from which the clinical material was selected, a total of 300 urethral strictures was studied A large portion of these patients had been under observation in this clinic for a number of years and had received various forms of therapy The average age of the patients was 64 5 years and 64 per cent were in the seventh and eighth decade of life The location of the stricture was identified in 210 patients by urethrograms and the remainder by urethral calibration (table 1)

The complications resulting from these urethral strictures were distributed throughout the proximal urinary tract The primary factor was obstruction to the flow of urine with secondary superimposed infection (table 2)

When the patients were first seen, calibration of the urethra revealed that 104 cases had strictures greater than 12F while 177 were less than 12F In 19 cases filiforms could not be passed and suprapubic cystostomy was required to establish urinary drainage In each instance where it was feasible, intermittent, gradual dilatation of the urethra was initiated Under this regimen, 130 patients improved (table 3) Their symptoms disappeared and the caliber of the urethra was maintained at 18–22F with periodic dilatations every four to nine months An additional 80 patients had relief of their difficulty in voiding but the caliber of their strictures could not be improved even with periodic dilatations as frequently as 2–3 months However, there was sufficient symptomatic relief to warrant continued dilatation in preference to operative intervention

In the remaining 90 patients, dilatation of the urethra produced inadequate results The patient's symptoms continued unabated and the urethral stricture became even tighter than on the initial examination Complicating infectious processes and urinary fistula developed Sixteen cases within this group had an internal urethrotomy but the end result was discouraging There was transient improvement in the caliber of the urethra and ease of dilatation Eventually, however, in all longer, tighter strictures developed than the original contractures Seven cases underwent external urethrotomy but the final result was similar

Five patients with marked urethral stricture were maintained on urethral catheter drainage because of their age and poor general health This form of therapy was utilized only in the extremely poor risk patients because of the large percentage of complications such as periurethral abscess, epididymitis and prostatitis which usually follow its inception

Permanent suprapubic catheter drainage was utilized in 25 cases for relief of

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TABLE 1 *Location of stricture*

	Gonorrheal	Trauma		Congenital
		Internal	External	
Penile	18	65	none	1
Penile—bulbous	21	32	2	1
Bulbous	40	34	11	1
Bulbomembranous	18	25	7	1
Membranous	2	7	none	none
Penile—bulbomembranous	6	6	2	none
Total 300	105	169	22	4

TABLE 2 *Complications*

	Cases
Pyuria	116
Chronic prostatitis and epididymitis	61
Episodes of complete urinary retentions	52
Hydronephrosis	23
Bladder calculi	22
Nonfunctioning of kidney on excretory urogram	20
Perineal abscesses with fistula	18
Pyelonephritis	15
Uremia	14
Renal calculi	13
Bladder diverticula	12
Ureteral reflux	9
Urethrorectal fistula	1
Renointestinal colic fistula	1

TABLE 3 *Results of therapy*

		Cases
1 Urethral caliber improved by dilatation		130
2 Urethral caliber maintained by dilatation		80
3 Urethral caliber unable to be maintained by dilatation		90
a Urethroplasty	60	
b Suprapubic cystostomy	25	
c Indwelling urethral catheter	5	
Total Cases		300

urinary obstruction These patients failed to respond to dilatation of the urethra and were either too old for plastic repair or by their own decision did not wish to undertake the operative procedures

The remaining 60 patients who did not respond to urethral dilatation and whose strictures decreased in caliber had a urethroplasty by the Johansen-Denis Browne technique

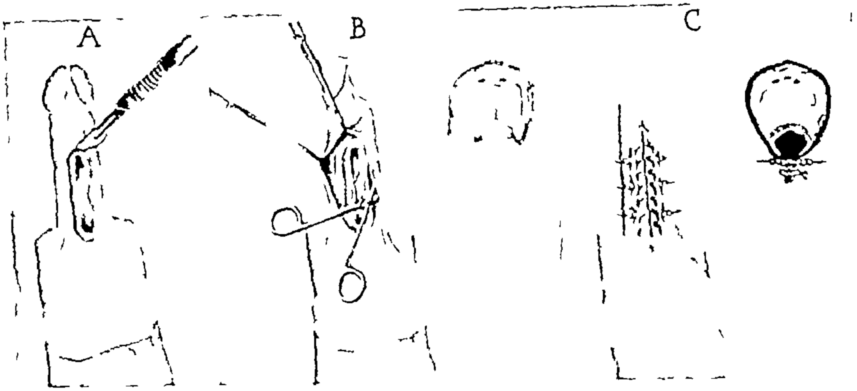

Fig 2

should enter these openings freely The remaining edges of the urethral mucosa and skin are then approximated with interrupted sutures along the incised ventral defect (fig 1, *D*) An indwelling Foley catheter is inserted in the proximal opening for urine drainage during the immediate postoperative period If the corporal bleeding has been well controlled by the sutures, a loose dressing is applied Occasionally there may be prolonged oozing from the corpus spongiosum which requires the application of a firm pressure dressing The indwelling catheter is removed on the seventh postoperative day and the patient allowed to void through the artificial hypospadias The second stage is not undertaken until the strictured area has epithelialized This usually requires six to eight weeks depending upon the degree of inflammation and fibrosis of the urethral wall and corpus spongiosum

The reconstruction of the urethra consists of burying an intact strip of epithelium which is composed of the original urethral mucosa and a thin strip of adjacent skin The width of this strip should be approximately ⅔ the circumference of the normal urethra (2–3 cm) An incision is made around the defect on the ventral surface of the penis, including the proximal and distal urethral openings (fig 2, *A*) The lateral margins of the incision are widely undermined in all directions (fig 2, *B*) The flaps created by this manipulation are drawn over the intact strip of epithelium and closed so that a wide portion of their raw surfaces are in contact This is accomplished with deep wire sutures which are held in place with double lead shot Reinforcing vertical mattress chromic catgut sutures are used between the wires These sutures should not be applied too tightly for postoperative edema may produce necrosis, with subsequent fistula at the site of the sutures (fig 2, *C*)

When the stricture involves the entire distal portion of the urethra, the straight scissors are inserted into the meatus and the urethra opened along the ventral raphe until the normal proximal urethra is encountered (fig 3, *A*) The edges of the urethra and skin are approximated as described above (fig 3, *B* and *C*) In the reconstruction of this type of defect, an incision is made through the skin around the proximal urethral opening and continued towards the glans in parallel lines leaving a strip of epithelium Two triangular flaps are created by

OPERATIVE TECHNIQUES FOR STRICTURES DISTAL TO THE PENOSCROTAL JUNCTION

In order to localize the distal end of the stricture, a large (24–26F) curved sound is passed into the urethra until obstruction is encountered (fig 1, *A*) While an assistant holds the penis in an extended position and supports the sound in the urethra so that the tip of it is toward the ventral surface of the penis, an incision is made through the skin, underlying supporting tissue, Buck's fascia, corpus spongiosum and urethral wall The edges of the urethra are then accurately approximated to the skin edges with fine interrupted chromic catgut sutures (fig 1, *B*)

The remainder of the stricture and ventral surface of the penis are incised in the midline until the normal proximal urethra has been attained At this point the urethra and skin edges are accurately approximated as at the distal end of the stricture (fig 1, *C*) The proximal and distal ends of the incised urethra must be accurately approximated to prevent contracture of the orifices A 26F sound

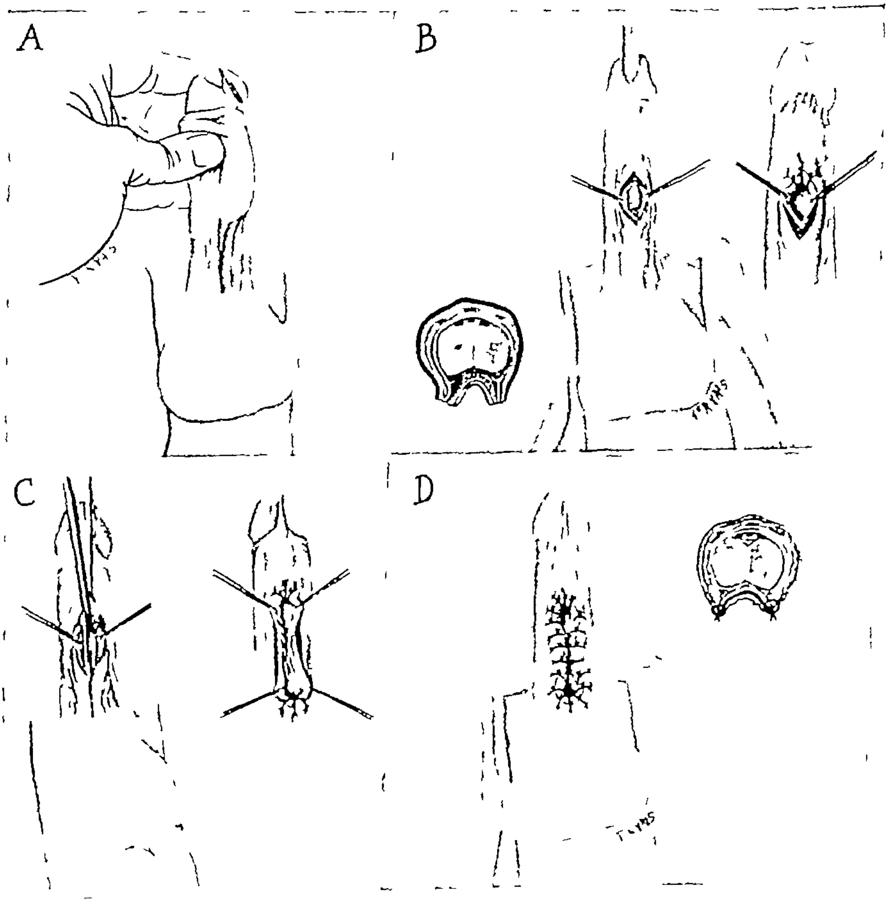

Fig 1

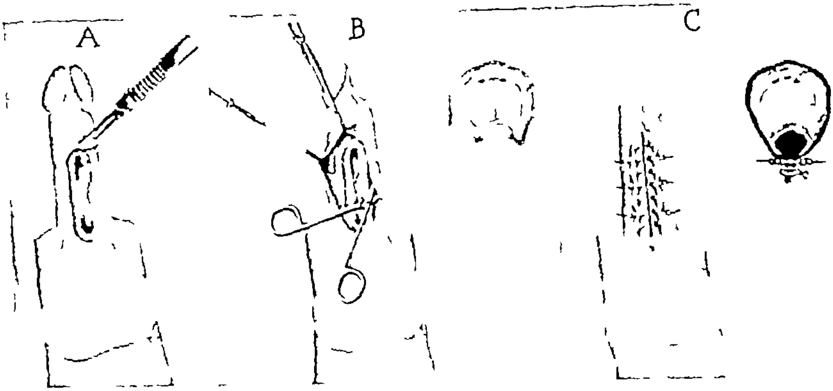

FIG 2

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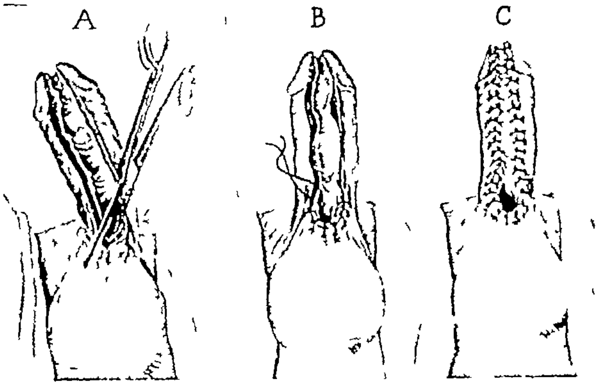

FIG 3

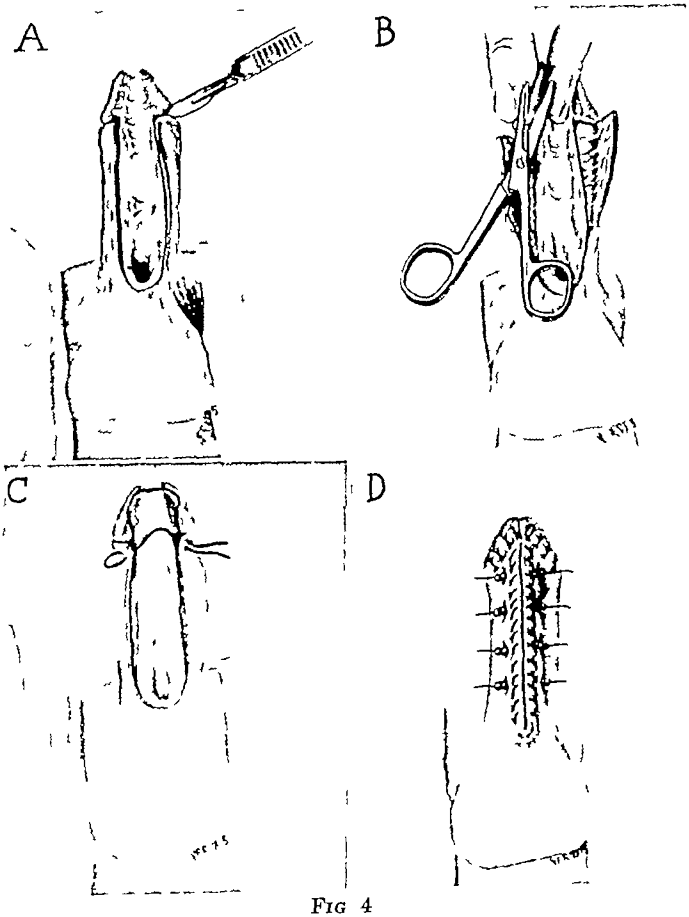

FIG 4

extending the incision in a circumferential manner just behind the corona (fig 4, *A*) These flaps are widely undermined A triangular area of the glans is denuded of epithelium so that the tips of the flaps may be brought to the tip of the glans (fig 4, *B*) In order to move the bilateral triangular flaps to the tip of the glans and at the same time approximate their raw surfaces, a mattress suture is used which enters one flap near its angle, and the lateral border of each of the denuded areas of the glans, before entering the angle of the opposite flap The suture is then passed through the angle of each flap again completing the mattress suture (fig 4, *C*) The remainder of the flap is sutured to the lateral edges of the denuded area of the glans and to the opposite flap, burying beneath it a strip of epithelium This is accomplished with interrupted vertical mattress chromic catgut sutures and wire sutures double stopped with lead shot (fig 4, *D*)

OPERATIVE TECHNIQUE FOR STRICTURES PROXIMAL TO THE PENOSCROTAL JUNCTION

The principles are the same for strictures proximal to the penoscrotal junction, but the technique of the operative procedure is different The skin which is sutured to the urethral mucosa is derived from the scrotum and is used in preference to perineal skin because it is more movable and assures sufficient epithelium to create adequate flaps to cover the buried epithelial strip, when completing the construction of the urethral canal

The deeper or more proximal urethral strictures are exposed through a curved incision in the anterior or urogenital triangle of the perineum The bulbocavernosus muscle is separated in the midline and retracted laterally, exposing the bulbous portion of the corpus spongiosum The area of the stricture is identified by passing a curved sound in the urethra until it meets obstruction The sound is palpated and an incision made through the corpus spongiosum and the urethral wall at the distal end of the stricture exposing the sound The remainder of the stricture is opened until the normal calibered proximal urethra is attained (fig 5, *1*) When the stricture lies deep in the perineum, considerable aid is derived by the passage of a sound in the urethra from the bladder It helps to identify the proximal limitations of the stricture and insures accurate placement of the sutures in the proximal angle of the urethra

After the urethral stricture has been opened, a longitudinal incision is made in the scrotal raphe, the length of which corresponds to the length of the incision in the urethra (fig 5, *1*) The scrotum and perineum are widely undermined until the incisions communicate This leaves a bridge of intact perineal skin (fig 5, *2*) The scrotum is then turned under the perineal bridge of skin and brought into the perineum (fig 5, *3*) The lower angle of the scrotal incision is accurately approximated to the proximal normal urethra with fine chromic catgut sutures (fig 5, *4*) The upper angle of the scrotal incision is sutured to the distal angle of the normal urethra in a similar manner while the skin edges of the scrotal flap are sutured to the edges of the urethral mucosa for the entire length of the open urethra (fig 6)

This creates a funnel shaped defect in the scrotum which extends down to the

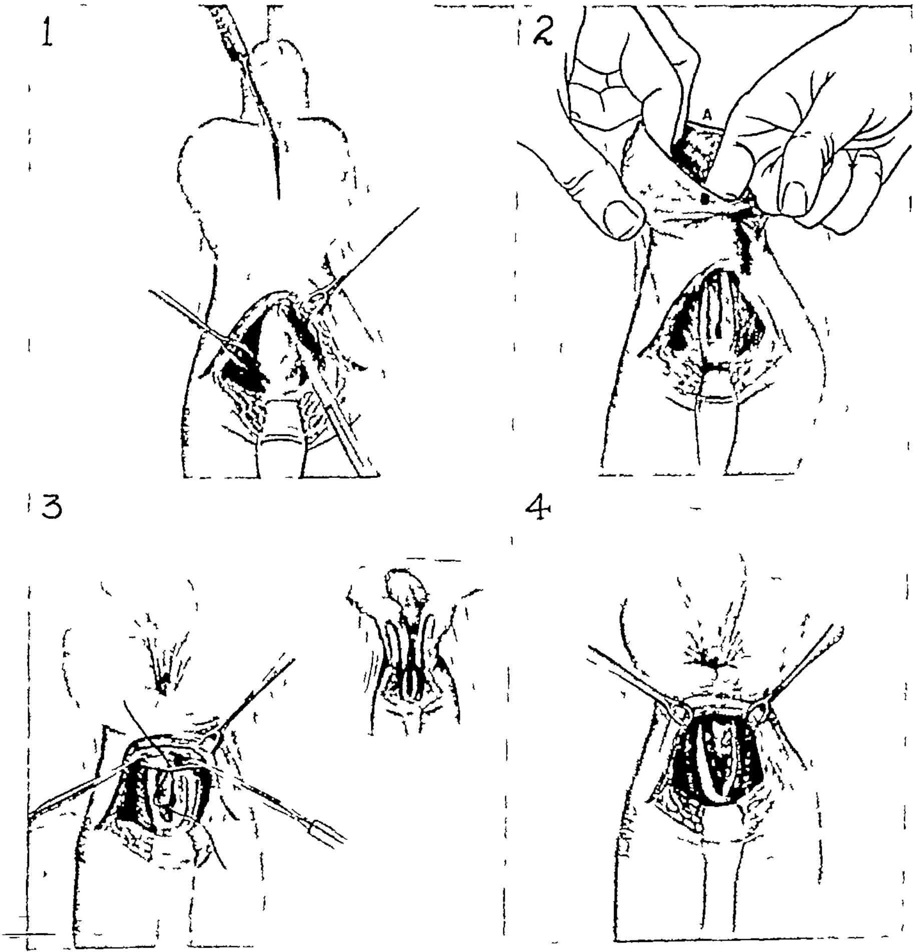

Fig 5

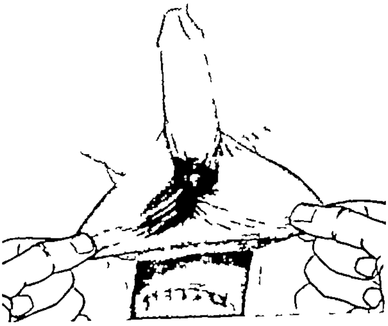

Fig 6

open urethra The perineal incision is closed by approximating the bulbocavernosus muscle over the scrotal flap followed by the subcutaneous tissue and skin An indwelling catheter is inserted through the funnel defect in the scrotum into the urethra and bladder to provide adequate postoperative urinary drainage A pressure dressing is applied After approximately one week, the urethral catheter is removed and the patient allowed to void through the artificial hypospadias

Reconstruction of the urethra is undertaken after the original strictured area has completely epithelialized Calibration of the proximal and distal urethral openings should be performed to be certain that scarring has not decreased their lumens If such has occurred, a revision of the angle should be performed prior to reconstruction of the urethra, or another stricture will result Occasionally bridging occurs between the lips of the original strictured urethra This must also be corrected prior to reconstruction of the urethra

After a patency of each urethral opening has been insured and the stricture has healed, reconstruction of the urethra is carried out An incision is made around both of the urethral openings and the defect in the urethra leaving a plate of epithelium 2–3 cm in width (fig 7, *A*) The lateral margins of the incision are widely undermined and closed over the buried plate of epithelium as previously described (fig 7, *B* and *C*) During the reconstruction phase, the urine must be diverted If the stricture was located in the distal urethra, either perineal urethrostomy or suprapubic cystostomy is utilized, but when the proximal urethra is the seat of reconstruction, suprapubic cystostomy is preferable Perineal urethrostomy may injure the scrotal flap and lead to necrosis and recurrent stricture of the urethra

In the majority of instances, a period of 9–10 days is required for the buried epithelial strip to epithelialize into a tube If the catheter diverting the urine becomes blocked or is accidentally expelled prior to complete healing, urine will extravasate beneath the flaps This extravasation may produce a periurethral abscess and subsequent urethral fistula Therefore, the diverting catheter is clamped after 9 days and a trial of voiding through the reconstructed urethra is permitted If extravasation occurs, the urine is manually expressed through the urethra and urinary diversion continued for an additional 5–6 days Generally, however, complete tube formation has occurred at the end of the initial period of

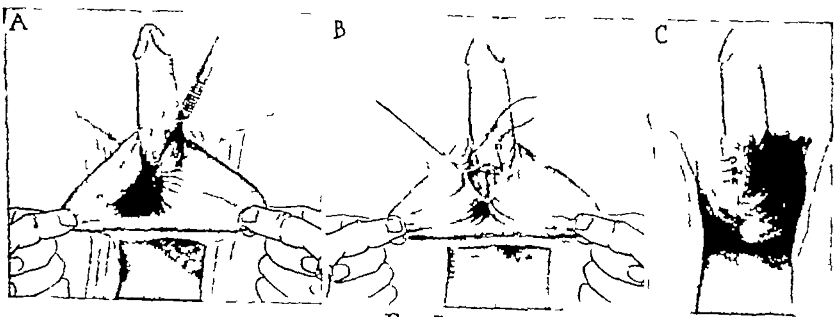

Fig 7

urinary diversion and the patient is able to void through the urethra without difficulty

RESULTS

All the patients were markedly improved following completion of their operations Periodic dilatations were no longer necessary The caliber of the urethra was improved and the patients voided with a good size and force to their stream Evaluation of the results was obtained by urethral catheterization, urethrograms and the time required for the patient to void 300 to 400 cc of urine No attempts were made to determine the maximal caliber of the reconstructed urethra for fear of tearing it and initiating a series of events which could lead to another stricture Instead we used a 22F soft rubber catheter and if this passed with ease, the urethra was considered to be of adequate caliber In addition, postoperative urethrograms were obtained in 43 patients, and in each case the urethral caliber was markedly improved and its outline relatively smooth (fig 8, *A*) A few patients were also evaluated by filling the bladder with 300 cc of normal saline and recording the time required to empty the bladder The majority were able to evacuate this volume in 15 seconds while one patient required only 7 seconds (fig 8, *B*)

Urethroscopy was performed on 9 patients Three of these had transurethral operative procedures performed in the bladder or at the bladder neck The resectoscopes (24–28F) passed with ease in each instance and no difficulties were encountered during the operative procedures or postoperatively Urethral hair was observed in 4 patients but so far no complications have arisen from its presence

A total of 125 operations were performed on 60 patients These consisted of 60 first stage procedures and 53 second stage operations Seven patients were satisfied with the marked improvement in voiding following the first state, so that they were reluctant to complete the operative repair These patients have continued to void through the artificial hypospadias opening with ease and have required no further instrumentation Eight patients required revision prior to undertaking the second stage Constriction at either the proximal or distal

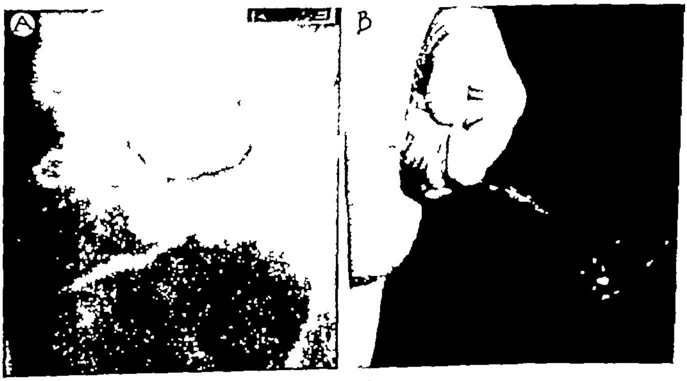

FIG 8

opening in the urethra necessitated each of these revisions Inaccurate approximation of the skin edge and urethral mucosa, separation of the suture line and bridge formation between the two edges of the ulcerated infected urethra were responsible for the fibrosis which narrowed the artificial hypospadiac openings The technique utilized to revise the recurrent strictured areas was similar to the original first stage procedure

Likewise, revision of the second stage was necessary in 4 cases in which urine had extravasated beneath the undermined lateral flaps when the side tracking catheter became blocked or when epithelialization had not completed the tube by the time the patient was allowed to void through the new urethra Pockets of urine collected beneath these flaps and produced an abscess or fistula If this complication is recognized immediately serious consequences can often be avoided by manually expressing the extravasated urine from beneath the flaps and continuing the diversion of urine for several days Postoperative edema, insufficient undermining of the lateral skip flaps and poor control of hemorrhage also contribute to failures of the second stage repair by producing periurethral abscesses, fistula or partial or complete disruption of the wound

Six patients have expired but none as a direct result of the operative procedures Three died of coronary occlusions, one of cerebral vascular accident, one of carcinoma of the bladder and one of carcinoma of the prostate

SUMMARY

This study presents the experience in management of 300 cases of urethral strictures which were seen in a 2-year period at the University Hospitals All strictures were studied in regard to etiology, location, complication and their response to various forms of therapy

From this group 130 patients had improvement in symptoms and caliber by periodic urethral dilatations In 80 patients the obstructive symptoms were relieved but the caliber of the stricture was not improved In the remaining 90 patients dilatation proved to be inadequate The urethral caliber decreased and complications occurred Other forms of therapy such as internal and external urethrotomy were used but results were discouraging In 60 cases a Johansen-Denis Browne urethroplasty was utilized and proved to be of definite value in the control of the stricture and the complications All had marked improvement and did not require further dilatations The technique of the operative procedure has been discussed and illustrated in detail

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THE EFFECT OF ANTIBIOTICS UPON THE COURSE OF NON-GONOCOCCAL URETHRITIS

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PART 1 THE COURSE OF NON-GONOCOCCAL URETHRITIS

Urethritis is a common disease in military personnel[1, 2] At times, in our experience the incidence has transiently exceeded thirteen-hundred cases per one-thousand men per annum, but the average rate here is approximately one-third of this In the Far Eastern theater, non-gonococcal urethritis (NGU) comprises about one-third of the cases of urethritis The magnitude of the problem has stimulated clinical investigation by several authors,[1-6] embracing over three-thousand cases These reports accurately describe the epidemiology and acute clinical picture of the disease as well as evaluating a number of therapeutic regimens Most, however, tabulate their results on the basis of short followup periods, seldom over two weeks In only a few series are adequate controls available Harkness[7] does describe the course of the disease but uses nearly all treated individuals This phase of the project is designed to observe a group of NGU patients treated only with hygienic measures for a period of ten weeks It is felt that the information observed about the course of NGU treated in this fashion will serve as a basis of comparison for other therapeutic programs

Methods All patients in the series were permanently stationed at a large military installation in Central Japan Each presented at sick call complaining of a urethral discharge Gram stains of the discharge on two successive days demonstrated pus cells with or without bacteria, but failed to reveal gonococci or H ducreyi Patients not confessing to recent sexual exposures and with histories of either penile manipulation or heavy alcoholic ingestion were eliminated from the series Although the place of these factors in the etiology of the NGU is obscure, several authors[1-5] have suggested that a non-infectious inflammation may be present under these circumstances In view of the reported high incidence of congestive prostatitis in young, apparently healthy men,[8] prostatic massages

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were not routinely performed unless the patient had suggestive symptoms When such symptoms were present, and prostatic examinations with smears were positive, the patients were not included in the series It has been previously reported that patients with NGU have no unusually high incidence of prostatitis[9] Signs or symptoms of prostatitis, however, appearing after beginning the therapeutic program for NGU were considered as complicated NGU

Although the rationale is not clear, it has been the clinical impression of most authors dealing with NGU that certain hygienic measures will improve cure rates In order to secure patient co-operation and to obtain a uniform background against which additional therapy could be evaluated, certain hygienic measures were imposed on all patients in this series In addition to avoiding alcohol, coffee, and carbonated beverages for four weeks, the patients were instructed to refrain from sexual intercourse or self-examination ("milking-down" the urethra) during the entire ten week period of observation The patients were also reassured that their disease was not serious and that it would respond to treatment A placebo tablet was administered twice daily for ten days, and the patients were seen two, four and ten weeks after beginning therapy Patients with urethral findings at the fourth week were given one gram of aureomycin daily for four days or one gram of streptomycin and four grams of sulfadiazine daily for four days Those unresponding to systemic measures were given silver nitrate in a dilution of 1 200 intraurethrally at the tenth week A routine serologic test for syphilis was performed at the final visit

Patients were omitted from the series if they transferred to other areas or received antibiotic therapy for unrelated diseases Determination of how closely the patients followed the hygienic regimen depended entirely on their own statements Occasionally violations were reported by the patients, admittedly many more occurred but were not confessed Because of the uncertain basis for avoidance of alcohol, coffee, and carbonated beverages, admitted violations of these prohibitions were handled by reprimanding the patients but retaining them in the series Usually, recurrences of persistent discharges were not associated with these episodes If, however, they developed a gonococcic or non-gonococcic discharge after having sexual exposure, they were excluded from the series Although elimination of this group improved the results of treatment, perhaps unfairly, it was felt that the course of the disease could not be "isolated" in any other way A similar procedure was followed in a comparative series with different therapies, and it was felt that this recurrent group would be uniform for all treatment regimens One-hundred and twenty-three patients were initially treated for NGU Eighty completed the program, twenty-seven transferred to other areas, three re-acquired a non-gonococcic urethral discharge after sexual contact, seven developed gonorrhea from re-exposure, one had chancroid after re-exposure, and five received antibiotics for unrelated diseases

Results Of the 80 patients given placebos, sixty-six were free of their discharges within two weeks Three additional patients completely remitted between the

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[9] O'Shaughnessy E J, Parrino, P S and White J D Chronic prostatitis Fact or fiction J A M A, 160 540-542 1956

TABLE 1 *Therapeutic results*

Group	Number	Per cent cured with one course of therapy in ten weeks	Per cent cured only after one additional course of treatment	Per cent with discharge at tenth week*		Per cent complications
				Late relapse	Persistent discharge	
Placebo	80	67	15	4	9	5
Pyridium	63	81	10	3	3	3
Aureomycin	60	70	13	14	3	0
Streptomycin and sulfadiazine	49	76	8	12	2	2

* Patients with a persistent discharge had received at least one course of therapy in addition to the initial treatment Patients with late relapses redeveloped their findings late in the 10 week observation period and therefore had received no medication other than the initial treatment

second and fourth week However, in 11 patients in this group a recrudescence of discharge developed during the fourth week of treatment, all after an asymptomatic period of 3 weeks Twenty of 22 patients with discharges at the fourth week received antibiotics, 12 recovered, one cleared temporarily only to later have a complication develop, but seven others required further therapy with silver nitrate intraurethral instillations before the discharge remitted In the other two with discharges complications developed during the fourth week Not previously receiving antibiotics, two with only sporadic discharges later acquired persistent discharges which ceased after antibiotics were given at the final examination, a third who relapsed after eight asymptomatic weeks also remitted after antibiotics

In 4 patients, three mentioned earlier, complications of the disease developed All had prostatitis, two had epididymitis as well Two complications (one prostatitis and one prostatitis with epididymitis) developed in the group with persistent discharges In the other 2 patients complications developed during the eighth week after 4 and 7 weeks without any evidence of urethritis All complications responded readily to antibiotics

With particular interest we noted, as have other authors,[5] that several patients (21 per cent) had transitory periods free of discharge only to be followed by relapses But when patients were asymptomatic after 1 month of treatment, in only three did an unremitting discharge develop later Twenty patients received one of the antibiotic regimens but seven failed to clear until silver nitrate instillations were given Therefore, these patients were refractory to antibiotics as well as to the hygienic measures To refute any belief that observation without antibiotics might produce a resistant discharge, other observers[4, 10] stated that in their series the duration of symptoms prior to therapy did not affect the chance for recovery

Sixty-seven per cent of the patients completely remitted without complications in 10 weeks Fifteen per cent cleared only after antibiotics and an additional 4

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[10] Ambrose, S S and Taylor, W W Study of etiology epidemiology and therapeusis of non gonococcal urethritis Am J Syphilis, Gonorr and Venereal Dis , 37 501–513, 1953

per cent who relapsed late appeared to respond following antibiotics Nine per cent with persistent discharges even after antibiotics required silver nitrate instillations before clearing In 5 per cent some complication of NGU developed

Discussion Most studies[1 3 11] which present a significantly large group of NGU patients were taken from large transient military centers where the patients could not be detained for prolonged followup periods of observation Although in most series the number of control patients for the antibiotic treated individuals has been small, several authors have mentioned relatively large groups of patients with NGU who were briefly observed without antibiotic therapy Of his 180 NGU patients, Grenley[12] noted that 30 per cent resolved in 3 days after an initial non-gonococcic urethral discharge was detected Following the 3 day observation period, the remaining cases were given sulfa and the discharge ceased He does not mention following them after their discharges disappeared Prostatitis developed in three and in one, epididymitis[12] After 2 weeks' treatment with placebos, 13 per cent of Jensen's[4] 68 patients were cured, another 11 per cent were free of findings in 1 week but were not followed further Out of Parrino's[4] forty-seven placebo treated NGU patients, 45 per cent were free of disease in 10 days Stressing the importance of the previously mentioned hygienic measures, Logue[13] pointed out that 26 per cent of his 141 NGU patients were symptom free in 48 hours without antibiotics Since discharges present for more than two days were treated with antibiotics, the incidence of later spontaneous remissions could not be determined These articles described patients with urethritis followed for short periods who became free of symptoms without antibiotic therapy In another series[5] longer followup periods were utilized, however, the relatively small number of patients reduces its significance Here, after 4 weeks five of twelve placebo treated NGU patients were well, another three were definitely improved Experience has shown us, as it did Wolf,[5] that the disease may have a prolonged course which is subject to spontaneous remissions or relapses Therefore, an accurate evaluation of any therapeutic program as well as lucid description of the disease should include a prolonged period of observation

The percentage of patients cured in this series appears somewhat higher than in the previously mentioned groups treated without antibiotics The apparent discrepancy may be due to one or a combination of factors Although most of the definitely incriminated agents were eliminated in each study, the etiology of NGU in the greatest number of cases remains unproven[1 3 10 14 16] It would thus be impossible to determine if the causes were the same in each series

With considerable interest we noted that reassurance and a simple hygienic program seemed to be more successful than previously appreciated The effect

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[11] Crouch, R D , Reese, J E and Boudreau, H J Non gonococcal urethritis in Korean rotatees U S Armed Forces Med J , 4 1159–1165, 1953

[12] Grenley, Philip Non specific urethritis of venereal origin J Urol , 52 92–97, 1944

[13] Logue, J T and Bird, F L Purulent urethritis U S Armed Forces Med J , 5 186–188, 1954

[14] Willcox, R R Researches in aetiology of non specific urethritis Brit Med J , 1 13–15 1954

[15] Willcox R R The etiology of non gonococcal (non specific) urethritis J Chronic Dis , 1 381–391 1955

[16] Day, C H and Arm, H G Clinical and bacteriologic studies on non gonococcal urethritis J Urol , 74 202–206, 1955

may be mediated by removal of non-specific irritants that have been implicated in the causation of NGU Patients were given an active part in the therapy, they were instructed that the medication was no more important than their observance of the rules Also, they were reassured that the disease was not gonorrhea, that complications were uncommon, and that although the disease was occasionally slow to heal it would gradually clear up These instructions prepared the patients psychologically for a potentially prolonged course and reduced fearful concern about their genitalia Under these circumstances, spontaneous healing could well occur Parinno[1] also stressed the therapeutic importance of a healthful attitude toward NGU However, despite the apparent success of the hygienic program and a healthy mental attitude, the value of these measures was not completely tested It was not feasible to require a control group, empirically selected, to deliberately indulge in practices which would violate the hygienic program In several patients transitory urethral discharges developed after the ingestion of alcohol or large amounts of coffee, however, these symptoms nearly always disappeared when the hygienic program was again obeyed Since the disease usually gradually ceased spontaneously even in several patients who admitted to disregarding various parts of the program, the self-limited nature of NGU may have well been the most important factor

Because re-infection could not be definitely eliminated, re-exposures with resultant discharges were not included Early it was feared that their omission might unjustly improve the results, however, observation did not prove this to be true Of these recurring urethral discharges one-third were non-gonococcic Since this is about the same proportion as occurred among the originally acquired discharges, it would seem reasonable to assume that the discharges represented new cases and not exacerbations of previously acquired NGU

Summary NGU is a low grade, generally self-limited, inflammatory proce with a purulent or mucopurulent discharge It is typified by periods of appare complete remission only to be followed by subsequent relapses, and approximately two-thirds of the cases clear spontaneously without antibiotics In a relatively small number of patients complications develop

PART 2 THERAPY OF NON-GONOCOCCAL URETHRITIS

Antibiotics are generally accepted as the preferred agents for treatment of non-gonococcal urethritis (NGU) The medications are used widely but their effect is observed for relatively short periods, ordinarily not over two weeks Preliminary studies reveal that NGU usually is self-limited and that the disease is subject to remissions and exacerbations Consequently, an accurate demonstration of the value of a drug should require that the treated patients and an adequate number of control patients be observed for a prolonged period

As with many types of medications antibiotics initially were used enthusiastically in almost every type of illness, however, experience has shown that they have not always been necessary or even advantageous [17] [18] Because of this more recent concept, the effect of antibiotic therapy upon the course of NGU will be studied in this part of the paper Previously described placebo treated patients will provide the pattern for the natural course of the disease, and in order to gain additional information about non-antibiotic treated patients a urinary tract analgesic will also be evaluated

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[17] Kagan B M and Faller Lucille Untoward reactions to antibiotics Med Clinics of North Amer , 39 111-124, 1955

[18] Carroll, Grayson Changing flora in urinary infections in this antibiotic age J Urol , 73 609-612 1955

Methods Patients were impartially selected with a similar group of NGU patients described in part 1 of this paper In order to accurately evaluate therapeutic results, the previously established hygienic program was utilized to afford a uniform background, then the NGU patients were divided into three therapeutic groups One-third of the group received pyridium, a mild urinary tract analgesic, 1 tablet 3 times a day for 4 weeks, one-third were given aureomycin 1 gm daily for 4 days, and the remainder received streptomycin 1 gm with sulfadiazine 4 gm daily for 4 days Patients with definite urethral findings at the fourth week were given additional therapy, usually a course of a different systemic drug Some patients, especially those with discharges resistant to oral medication, were treated with intraurethral instillations of silver nitrate (1 200)

A total of 391 patients began this program One hundred and seventy-two patients completed the study, one hundred and seventy-two transferred to other areas, thirty-five reacquired a non-gonococcic discharge after sexual exposure, eight acquired a gonococcic discharge from re-exposure, and four received antibiotics for unrelated diseases

Results Of the 63 patients given pyridium, fifty-one were free of their discharges after 2 weeks An additional six showed remission without further therapy between the second and fourth weeks Three patients relapsed during the fourth week, all after three asymptomatic weeks Nine patients then were considered treatment failures and received antibiotics Six cleared completely but one cleared temporarily only to have a complication develop later Two of the re-treated patients and an additional two patients who earlier had sporadic discharges later had persistent discharges develop and required still further therapy with silver nitrate instillations before recovery There were two complications, one prostatitis alone which was previously mentioned and one case of prostatitis with epididymitis, occurring after asymptomatic periods of 2 and 9 weeks respectively Response to antibiotics was prompt and complete During the 10 weeks of observation 9 per cent of the patients relapsed after transitory remissions Eighty-one per cent of the patients treated with only pyridium responded within ten weeks without complications Ten per cent cleared only after antibiotics, 6 per cent with discharges at the tenth week remitted after silver nitrate instillations, one half of these had failed to respond to antibiotics, and in 3 per cent some complication of NGU developed

Fifty-three of the 60 patients treated with aureomycin were free from their discharge 2 weeks after the beginning of therapy Two patients later remitted without additional therapy Five patients relapsed during the fourth week, all after three asymptomatic weeks Seven of 9 patients cleared completely after receiving streptomycin and sulfadiazine, another remitted after a single silver nitrate instillation In addition to the 2 patients who failed to respond to repeated courses of antibiotics, eight relapses occurred after asymptomatic periods of four to eight weeks. These discharges gradually ceased after repeated silver nitrate instillations. Following periods of apparent complete remission during the 10 weeks of observation, 22 per cent of the group relapsed. Seventy per cent of the patients treated with one course of aureomycin were free of their urethral discharge in 10 weeks without complications. Fourteen per cent cleared only after an additional course of therapy, 17 per cent with discharges at the tenth week, 3 per cent failing to respond to repeated courses of antibiotics, remitted after silver nitrate instillations, complications developed in none.

Forty-five of the forty-nine NGU patients treated with streptomycin and sulfadiazine became free of their findings by the second week. Another patient's discharge later completely remitted without additional therapy. Three relapsed during the fourth week after three asymptomatic weeks, one of these later spontaneously cleared. Three of four patients responded to a course of aureomycin, another resolved after a single silver nitrate instillation. Of the 7 patients with discharges at the tenth week, six had relapses after being free of definite findings for seven to nine weeks, one had failed to respond to aureomycin as well as to streptomycin and sulfadiazine. These patients eventually cleared after receiving pyridium or silver nitrate instillations. In one, prostatitis developed after he had been asymptomatic for 7 weeks, he resolved rapidly with additional antibiotics. During the period of observation 15 per cent relapsed after transitory remissions. Seventy-six per cent of the patients treated with only a single course of streptomycin and sulfadiazine responded in 10 weeks without complications. Eight per cent remitted only after an additional course of therapy at the fourth week, 14 per cent with discharges at the tenth week, 2 per cent failing to respond to two courses of antibiotics, cleared with additional treatment, and 2 per cent experienced some complication of NGU.

Pyridium appeared to be the most effective agent but statistically the cure rates were not significantly different between the pyridium and either group* receiving a single course of antibiotics. Also, although not statistically significant the placebo group's cure rate† seemed less. If the proportional differences between groups remained constant, the addition of 25 cases would have caused the pyridium treated group's cure rate to be significantly greater than the placebo's group.

In 7 patients (3 per cent) prostatitis developed, nearly one-half also had epididymitis. The incidence of complications in our antibiotic treated groups appeared less, not significantly* however, than in the combined placebo and pyridium groups. A more striking difference, also not significant†, was noted between the aureomycin and placebo treated groups. If the proportional difference remained constant the placebo group's complication rate would have become significantly greater with the addition of 44 patients. No known strictures were encountered in this series. The immediate complications of NGU appeared to be mild and readily controlled with antibiotics.

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* $P > 0.10$

† $P < 0.10 > 0.05$

Ninety per cent of the antibiotic treated patients remitted in 2 weeks while only 80 per cent of the patients not receiving antibiotics cleared in the same period However, a large number of the antibiotic treated group relapsed later in the course of the disease This was especially evident after the fourth week when 13 per cent of the antibiotic treated group exacerbated following several asymptomatic weeks, while only 3½ per cent of the patients not receiving antibiotics relapsed During the 10 week program the percentage of patients requiring treatment in addition to the initial therapy was about the same Also, the percentage in each group with a discharge after 10 weeks was similar

Discussion Multiple etiologies have been attributed as the cause of non-gonococcal urethritis However, after specific factors such as trauma, endogenous or exogenous irritants, carcinomatous, tuberculous, syphilitic or chancroidal lesions, and trichomonal infections have been eliminated, there remains a large number of urethridities for which no definite etiologic factor has been determined Certain bacteria, pleuropneumonia-like organisms, or viruses have been partially incriminated, but the evidence has not been conclusive and authors such as Parrino[3] and Willcox[2 14 15] have reported extensive studies in which the cause of the disease could not be found in the majority of cases Therefore, although further etiologic studies should be continued, routine laboratory methods have appeared to be of little value in the diagnosis of NGU, after gonorrhea and the previously mentioned specific factors have been eliminated

Most antibiotics have been utilized in the treatment of NGU, but the clinical results have not been uniform The duration of treatment usually varies from three to ten days but seems to show no relationship to the therapeutic results Authors have reported cure rates as low as 47 per cent for penicillin,[2 11] 47 per cent for streptomycin,[2 11 19] 70 per cent for terramycin,[16] 66 per cent for aureomycin,[4] 37 per cent for sulfadiazine,[2 11] 50 per cent for erythromycin,[16] and 70 per cent for chloromycetin [2] On the other hand, authors [3 6 11 12] (includes one of the previously listed workers) have claimed cure rates of over ninety per cent for groups treated with several of these drugs

Since the etiology of NGU in the majority of cases is not definitely known, the basis for selection of treatment must be determined from therapeutic experience rather than from the usual laboratory diagnostic tools The erratic results of empirically selected antibiotics suggest that their effect upon the disease should be more carefully investigated Therefore, these groups of antibiotic treated patients will be compared with similarly selected groups of patients treated with placebos and pyridium

Antibiotics and pyridium appeared to alter the course of NGU in different ways, but there was little difference in the final results Remitting earlier, the antibiotic treated patients also tended to relapse in somewhat greater numbers, especially after the fourth week of observation The significance of this finding was not entirely understood however, several observations about patient differences were noted

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[19] Pulaski, E J Streptomycin therapy of penicillin resistant and sulfonamide resistant specific and non specific urethritis J Ven Dis Information, 28 1–6, 1947

The same instructions concerning the hygienic program were given to both groups but the initial response of the urethritis to the medication apparently affected the patient's attitude In both groups not receiving antibiotics the discharge gradually diminished and the individual realized that the disease, as he was instructed, had a prolonged course The placebo treated patient was aware of health rule infractions because they frequently precipitated a slight exacerbation The pyridium treated patient's colored urine served as a constant reminder of his disease, the analgesic action relieved his symptoms Antibiotics, in contra-distinction, usually rapidly removed the findings and symptoms Several individuals confessed that their early remission, after the antibiotics were administered, gave them a false sense of recovery and that they then disobeyed the hygienic rules Despite the ill understood rationale and poorly controlled nature of the hygienic program, violations of it in these patients often resulted in reappearance of a discharge Most of these cleared again when alcohol, coffee and local trauma were discontinued

A much higher proportion of the antibiotic treated patients, whose cases were eliminated from the study because of another urethral discharge developing after sexual exposure, had acquired a non-gonococcic discharge Therefore, if omission of this group unfairly improved results in the group of placebo treated patients, the factor was magnified for the antibiotic treated group Of the recurring urethral discharges 80 per cent were non-gonococcic Since it was previously noted in part 1 that approximately 35 per cent of originally acquired urethritis and of recurrent discharges in the placebo series were non-gonococcic, it would seem inaccurate to believe that all of these recurrences were new cases Consideration of these cases as relapses would greatly reduce the final efficacy of antibiotics Of course no definite conclusion could be drawn from these observations, but the sexual excitement or trauma from intercourse may have produced some of the relapses Interpolation would suggest suggest about two-thirds of the NGU recurrences in the antibiotic treated groups were not due to re-infection

The value of initial antibiotic therapy followed by a delayed remission was difficult to evaluate However, it seemed unlikely that antibiotics altered the course of the four antibiotic treated discharges which persisted recurrently for two to four weeks after treatment only to later spontaneously remit

Although not significant the incidence of complications in our antibiotic treated groups appeared less The rate of complications in the placebo treated group was somewhat higher than in a series described in part 1,[17] but it was comparable to Gartman's[8] 2267 NGU patients In 7 per cent of these, posterior urethritis with prostatitis developed and in 1 per cent epididymitis or ascending infections developed These complications were relatively mild in ours and other workers'[1] experience Certainly, their ready response to antibiotics suggested that these agents may have prophylactic value

Pyridium was believed initially to possess bacteriocidal properties, but now the drug is regarded as an analgesic only The medication symptomatically relieves and psychologically supports the patient by soothing the urethral mucosa and coloring the urine Pyridium appears slightly more effective than placebos or a single course of antibiotics It is further noted that when individuals are observed for 1 month, then given additional therapy for persistent discharges, usually antibiotics, all groups of NGU patients have similar final cure rates

The wide usage of antibiotics has brought with it certain disadvantages As Kagan[17] pointed out, many mild to serious toxic reactions may be caused by antibiotics Since reactions may occur such as "serum sickness," anaphalactoid shock, gastrointestinal disorders, neurotoxic reactions, hemopoietic depressions, renal-toxic disorders, or hepatic degenerations, he believed that antibiotics should not be given when simple or no therapy was just as satisfactory Also, with the large amount of antibiotics dispensed, many resistant strains have developed,[18] thus reducing the number of utilizable antibiotics One worker [20] even reported 3 cases of NGU which were complications of oxytetracycline administration for gastrointestinal infections Because of these definite disadvantages of antibiotic therapy, we must carefully evaluate not only diseases which require antibiotics but also consider which diseases will remit without antibiotics

Antibiotics, then, do have a definite effect upon the course of NGU They tend to give a better initial response, they cure many resistant cases, and they probably prophylactically reduce complications But the rapid removal of symptoms fails to condition the patient to his disease, and he then returns to old habits which aggravate NGU The final cure rates over long periods apparently depend on many complicated factors Antibiotics, after a single course, cure few more than placebos and possibly not as many as pyridium Thus, the most important factor in the treatment of NGU is a program which will remove the patient from non-specific factors that aggravate and prevent spontaneous healing Also, antibiotics do impose certain hazards Ultimately the physician himself must decide whether the advantages are significant enough to warrant the use of antibiotics In our experience the deleterious factors of routine antibiotic administration are not compensated by these advantages Since antibiotics frequently are essential for therapy, it seems better to treat simply without these medications when possible

Summary A single course of antibiotics shortened the course of NGU in most patients but cleared no greater number of patients than placebos or pyridium When additional therapy, usually antibiotics, was given to the patients who did not get well in a few weeks, the eventual cure rates in all groups were the same Silver nitrate intraurethral instillations were helpful when systemic methods failed Patients not initially receiving antibiotics appeared to have a slightly higher incidence of complications, however, these complications were mild and cleared readily with antibiotics

Acknowledgement is made of the statistical assistance given by James M Davis, Lt Col USAF (MC)

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INDICATIONS FOR HORMONAL TREATMENT OF CRYPTORCHISM

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Hormonal therapy for the cryptorchid has been used for 25 years, but one cannot find among the numerous articles any paper which summarizes the indications for its use. The many favorable reports at the onset of hormonal therapy indicated that its use might replace the surgical orchiopexy. To a certain extent this attitude was justifiable, because the surgical orchiopexy at that time was successful only in about fifty per cent of the cases due to short cords and interference with the blood supply to the testis.

Although several hormones, such as estergin, androgin, pituitary and thyroid extracts, have been used, it is generally accepted that the hormone which supercedes all others is the hormone extracted from the urine of pregnant women. This anterior pituitary-like principle known as APL and pharmacologically as follutin-S is the hormone of choice and is the one universally used. The hormone is found in the blood and urine of the fetus, and is present for 5 days following birth, after which it practically disappears until puberty. The greatest quantity of the hormone appears during puberty, after which there is a gradual diminution until old age.

Normally the testicles descend into the scrotum during the latter months of pregnancy, and those that have not descended at birth have a tendency to descend at puberty, two periods when there is the greatest amount of the hormone present. The inference to be drawn from the natural existence of this gonadotrophic hormone and the time of the descent of the testis into the scrotum make it the most plausible factor initiating the descent of the testis. The real active force which causes the testis to pass through the inguinal canal to the scrotum is the milking action of the cremasteric muscle. This physiological action has been observed by Hart in the kangaroo rat. Lewis severed the nerve to the cremaster muscle in rats and failed to obtain descent of the testes. These experimental observations, when transposed to humans, are rendered more potent by the fact that boys who have an agenesis or a testis which has never passed the internal inguinal ring are found to have a flat and undeveloped scrotum, the result of maldeveloped cremasteric muscle. A boy who has a migratory testis, a pseudocryptorchid, or who at some time has had a descent of the testes into the scrotum will show development of the scrotum and cremasteric muscle on that side.

Our research on the pre-adolescent macaque monkey, which included the sectioning of the cord and scrotum on one side followed by sufficient gonadotrophic hormonal injections to produce descent of the remaining testicle, was accompanied by a widening of the inguinal canal, an enlargement of the cremasteric muscle, increased vascularity of the cord, increased size of the lymph spaces, enlargement of the muscle fibers of the vas, and heaping up of the epithelial cells lining its

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lumen Thus we have initiatory and developmental factors favorable for the descent of the cryptorchid

The indications for the hormonal treatment for the undescended testis depend upon the location of the testis, whether it is intra-abdominal, within the inguinal canal, ectopic, or whether it might be unilateral, bilateral or absent, whether complicated by a large hernia, hydrocele, or other abnormalities, such as hypothyroid adiposity, hypopituitary dystrophy, eunuchoidism, dwarfism, or pseudo hermaphroditism with bifid scrotum and hypospadias The male and female pseudohermaphrodites without palpable gonads may be differentiated by the cytological sex chromatin epithelial cell tests

Theoretically, the most favorable cases for the use of the hormone are the bilateral cryptorchids, because without obstruction to their course of descent, their most probable failure to descend was due to the deficiency of the hormone in utero These are the most difficult ones to treat primarily with surgery because of the short spermatic arteries The testis has never migrated, and its artery, no matter what its origin, has rarely had an opportunity to elongate sufficiently to reach the scrotum It has been estimated by several writers before the use of hormones that 20 per cent of the orchiopexies resulted in the loss of the testis because of surgical interference with the blood supply The testes in these bilateral cases are less likely to show anatomical dysgenesis than the unilateral cryptorchid, and offer greater percentage of potential physiological normal development than the unilateral cryptorchids Gross states that 79 per cent are spermatogenic

Other conditions in which hormonal therapy is advocated may be found in cryptorchids associated with hypopituitary, hypothyroid, eunuchoidism and dwarfism Many of these cases are treated by endocrinologists It seems to be the opinion that thyroid adiposities with gonadal dysgenesis should have thyroid treatment before or along with gonadotrophic hormone, and that the treatment be carried over a longer period of time using much larger amounts of hormone than for the uncomplicated cases These cases demand basal metabolism tests and a correction with extracts of pituitary or thyroid as needed Not all adiposity cases have thyroid deficiency for some only require limitation of calorie intake along with hormonal therapy These cases require the attention and services of both the endocrinologist and the urologist

In the case of unilateral cryptorchid, we have a different problem Both testes have been theoretically subjected to equal opportunities for descent by the action of the hormone in utero, and it would not be expected that more gonadotrophic hormone would induce a descent of these testes When one testis is retained and the other testis descends into the scrotum, we find at operation one of the many reasons as listed in our textbooks for the retention However, a majority of the unilateral cryptochids are ectopic testes or are associated with hernias and hydroceles These are not suitable cases for hormonal therapy However, there are some unilateral cryptorchids which are not palpated or they lie in the inguinal canal not associated with demonstrable hernia or hydrocele which should be selected for hormonal therapy

The most difficult testis to transplant surgically is the testis whose spermatic artery is of inadequate length The fact that these so-called short vessels have not been a problem subsequent to adequate hormonal therapy, that we have not had to leave such a testis in the inguinal canal for a later transplant, as some surgeons report, and lastly that for twenty years we have not had to do an orchiectomy because of insufficient length of cord, designates the importance of the hormonal application for these cases As an adjunct to technical surgical orchiopexy for the bilateral and unilateral cryptorchids with short spermatic arteries, there is no doubt about the value of the gonadotrophic hormone

The amount of the hormone to be used has been a subject for great debate and varies from a few hundred rat units to several hundred thousand units In 1934 Aberle and Jenkins, working on monkeys and later on humans, found that 1700 to 4000 units were required to cause a testis to descend into the scrotum An edema of the foreskin and scrotum almost always preceded the descent of testis by a few days For the average boy 3000 units given over a 4-week period produces this clinical picture Robinson and Engle have tried 4000 to 5000 units of chorionic gonadotrophin per day for three consecutive days and then operating if the testis did not descend Large doses over a long period of time produce precocious sex development, premature union of epiphyses and psychic disturbances, and some authors report a regression in the size of the testes Erlich has shown that testes which descend after large doses of hormone are uniformly aspermatogenic Therefore, it is necessary to set a limit for the amount of chorionic gonadotrophic hormone to be used For 20 years we have been using 250 units given intramuscularly 3 times a week for 4 weeks, and have experienced no adverse effects under this regimen

There is great variance as to the age of the child when hormone had best be used Many observers have expressed the view that the earlier the testis is placed in the normal position, the greater will be the opportunity for it to develop and become spermatogenic Charny and Wolgin have recently published the most comprehensive microscopic study of biopsies of the undescended testicles at various times, such as from birth through adolescence, after spontaneous descent, after hormonal administration, and during and following surgical orchiopexy They state that the testis shows three stages of development 1) resting phase from birth to the age of four years, 2) growth phase from four to ten years, and 3) maturation phase from ten years through adolescence Certainly if there is any virtue in transplanting the cryptorchid for the maintenance of spermatogenesis, it should be done early in the growth phase

Objections have been made against the use of the hormone because its administration caused more discomfort to the child than surgical procedure We have not had this experience Again, the cost of hormonal treatment has been criticized as being greater than the cost of surgical treatment If such were the case, then undue charges were made and are to be reprimanded In the use of the hormone the surgeon should always begin with a plan of therapy and execute the program precisely, followed immediately by surgery if the testis does not descend

Of the 204 cases of cryptorchism recorded in our series since the onset of hormonal therapy, 56 cases were particularly selected for hormonal treatment, 19 left, 20 right and 17 bilateral Successful results were obtained in three each left-

and right-sided, and two in the bilateral cases, equivalent to 14 per cent of the selected cases so treated

The hormone is of no particular value in cases with ectopic testis, migratory testis, pseudocryptorchids, agenesis of testis, cryptorchids associated with large hernias and hydrocele or in post-puberty cases

SUMMARY

The indications for hormonal use for cryptorchids is limited to a selected group, roughly about 25 per cent of all cases These cases include all bilateral and special unilateral cases, with the expectation of a small percentage of successful descents Its main value is calculated as an adjunct to surgical orchiopexy, for the selected group of cryptorchids which have short cords and inadequate spermatic arterial length to reach the scrotum

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UNDESCENDED TESTES: SURGICAL PROCEDURES

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The earliest attempts to bring the undescended testes to the scrotum were one-stage procedures. The first is attributed to Koch who, according to Rosenmerkel, in 1820, used a suture to fix the testis to the fundus of the scrotum. Schüller, in 1881, recognizing the need of lengthening the spermatic cord, divided the vaginal process, then placed the testis in the scrotum and anchored it with a stitch. Bevan, in 1899 and 1903, carried the principle further. He removed the vaginal process from the cord, separated the cord from the posterior peritoneum above the internal ring, and freed the vessels and vas from the constricting fibrous bands in the cord. Then he placed the testis in the scrotum without traction and placed a purse string suture at the top of the scrotum. In 1930, Ombrédanne did a one-stage transcrotal orchiopexy. In his operation the testis is placed on the opposite side of the scrotum and is held in place by means of the elastic septum between the scrotal compartments.

A two-stage orchiopexy was introduced independently by Keetley in England, in 1905, and by Torek in this country in 1909. In both operations the scrotum is fixed to the skin of the thigh and the testis is fixed to the fascia of the thigh. The two operations differed in that Keetley placed the anchoring suture through the gubernaculum, whereas Torek placed it in the tunica of the testis. In the second stage of each procedure the scrotum and the testis are released from their attachments to the thigh.

Wangensteen, in 1932, placed the anchoring suture in the testis after the manner of Torek, but brought only the suture to the fascia of the thigh and left the testis in the scrotum. In their procedure, McKenna and Ewert, in 1935, also left the testis in the scrotum, but like Keetley they sutured the gubernaculum to the thigh.

Kiefer, doing the same type of operation as that done by McKenna and Ewert in 1951, described a technique for mild continuous postoperative traction. It consisted of wrapping a small rubber tissue drain around the scrotal isthmus and attaching the drain to a rubber band stretched down and secured to the thigh with adhesive. In 1931, Cabot and Nesbit achieved adequate continuous temporary traction in their one-stage procedure by means of an elastic band attached to a stay suture passed through the lowest point of the gubernaculum.

Whether it is done by one or two stages, the basic principles of orchiopexy are: 1) dilatation of the scrotum for reception of the testis; 2) freeing the vessels of the testis and freeing the vas so that the testis can be positioned without tension; 3) high ligation of the vaginal process; 4) use of some means of fixation and traction so that the testis will remain in the scrotum.

As Scarpa's fascia is incised and the bursa freed from its attachments, at the

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Abstract of paper read at annual meeting of American Association of Genito-Urinary Surgeons, Osterville, Mass., June 5-7, 1956.

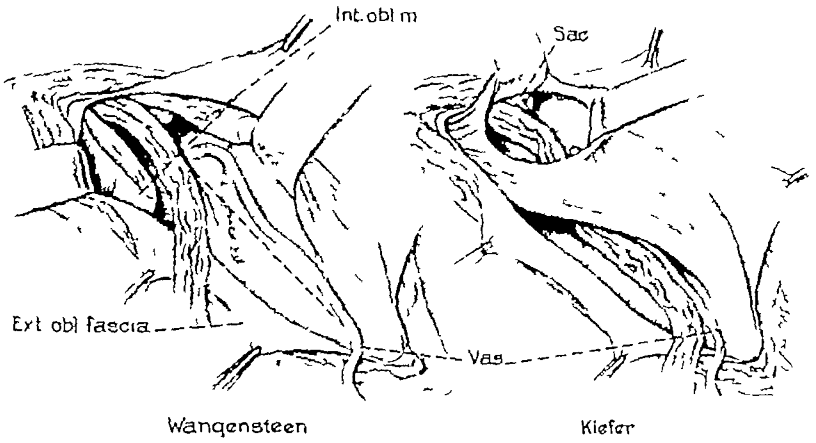

FIG 1 Procedure for facilitating retroperitoneal dissection of internal spermatic vessels In Wangensteen procedure incision is made across internal oblique and transversus muscle Broken line indicates incision in transversalis fascia Inferior epigastric vessels course below this fascia In Kiefer operation, muscle splitting incision is made in line of muscle fibers

beginning of the dissection, care must be taken not to injure the ilio-inguinal nerve After incising the external oblique fascia and mobilizing the cord, care must be taken not to injure the artery and veins as dissection progresses The extent of the dissection required is determined by the findings in the individual patient In some, minimal dissection liberates the vessels of the testis sufficiently to permit placement of the testis in the scrotum or anchoring it to the thigh without tension In others, considerably more dissection is necessary

Maximum length is achieved by first releasing the artery and veins of the cord from their constricting fibers and then freeing the internal spermatic vessels in their retroperitoneal course above the cord (fig 1) On occasions it is also necessary to carry dissection of the vas beyond its liberation from the cord Beginning the additional dissection at the abdominal inguinal ring, the vas is freed along its course over the epigastric vessels, near their origin from the external iliac artery and vein, and down the side wall of the pelvis toward the ischial spine

In some patients the cord structures remain too short for positioning of the testis despite maximum dissection Encountering this condition, Cabot and Nesbit, and later Gross, were able to bring the testis to the scrotum by a two-stage mobilization procedure At the first operation the testis is liberated as extensively as the situation permits and positioned at the lowest possible point At the second operation, a year or two later, further liberation is accomplished Schutt was of the opinion that if the cord is too short to allow placement of the testis in the scrotum, the scrotum should be brought to the testis, as is done in the Ombrédanne operation

These last mentioned procedures merit trial, particularly when bilaterally undescended testes with short cords appear to be normal Bringing the bilaterally retained testes outside the external rings and positioning them as low as possible will preserve at least Leydig cell function A unilaterally undescended testis with an excessively short cord should be removed Under no circumstances must a testis be put in the abdomen where it could not be observed for possible development of malignancy

Underdevelopment of the scrotum is considered by some surgeons to be an indication for the two-stage operation As administered today, hormone therapy aids in development of the scrotum, as well as the testes and cord structures, and thus eliminates this reason for the two-stage orchiopexy

Another reason given for doing a two-stage orchiopexy is that it will maintain the length of the testicular vessels achieved by the dissection However, in bringing the testis to the thigh undue tension may be exerted on its vascular supply Also, when the testis is subsequently freed from the thigh it is subjected to further manipulation In the one-stage orchiopexy the possibility of excessive tension is not so great because less cord length is required for positioning the testis And there is no need to manipulate the testis again Both these factors minimize operative trauma, and make the one-stage orchiopexy more desirable than the two-stage procedure Operative trauma adds to the possibility of irreparable damage to the testis

DISCUSSION

The current controversy regarding management of undescended testes is due not so much to lack of an adequate operation as to "the appropriate age" for surgical placement However, age becomes of secondary consideration when torsion or the symptoms from either a concurrent, clinically demonstrable hernia or a testis trapped in the superficial inguinal pouch demand surgical intervention Complications of this nature occur in many extremely young as well as in older children And when the complication is corrected the testis is also brought to the scrotum Thus, orchiopexy is often of necessity done early—even by surgeons who would otherwise defer it until just prior to puberty to avoid operating on the testis that will descend spontaneously and to have better developed tissues if operation is necessary

Today the surgeon no longer needs to wait to see if a testis will descend spontaneously With hormone stimulation he can in a short time determine which one will respond to the treatment and descend and which one cannot descend and will require exploration Spontaneous descent is prevented, chiefly, by congenital anomalies of the testis, its vessels and mesentery, or the structures forming the pathway of its descent Among the various anomalies are

1) Agenesis or rudimentary tissue, which explains most clinically impalpable testes

2) Failure of the funicular portion of the vaginal process to close, which it does in the normally descended testis shortly before birth or within a month thereafter (In each of 44 testes that descended spontaneously at ages 7 to 21, in a series I recently studied, there was no hernia on clinical examination, indi-

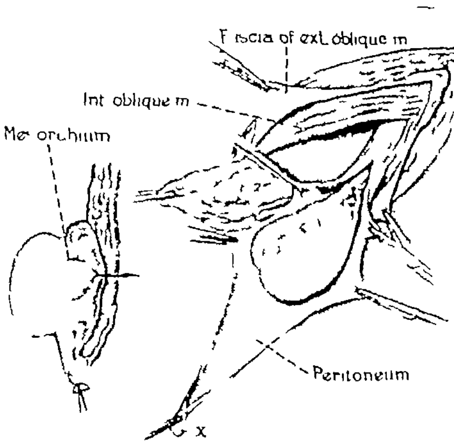

Fig 2 Elongated peritoneal sac which was directed toward perineum X, fibers of external spermatic fascia projecting beyond bursa Insert shows vas coursing in mesentery inferior to testis Danger of catching vas in suture through gubernaculum is evident

cating the vaginal process was closed But in 4 instances it subsequently opened and produced clinically demonstrable hernias at intervals varying from 6 months to 10 years after descent And at operations for removal of undescended testes in several adults, I observed the sac in each instance was completely obliterated)

3) Short cords

4) Lack of development of the external ring, partial or complete

5) Contracture of the neck of the scrotum

6) Deviation and abnormal attachment of the external spermatic fascia which forms the outermost investment of the bursa (fig 2)

In using the hormone as a diagnostic measure, it is important to give an amount large enough to insure descent of the testes in the absence of the anomalies enumerated From my experience, an adequate amount is 4,000 international units of chorionic gonadotrophin (Ayerst) 3 times a week up to 40,000 units Some testes descend before the course is completed But if the total 40,000 units fail to bring the testes down, repetition of the course will not induce descent

Under careful observation the total dose of 40,000 units can be given to a young as well as an older child without danger of untoward effects Nevertheless, even in the child with bilateral retention there would be no need to give the hormone until he is at least 5 because up to this age the retained testes are like their scrotal counterparts If there is no response within a month after the full course has been given, exploration should be done and the testes brought down if they are found But operation must not be done later than puberty, as established by the appearance of the first pubic hair

Despite histologic evidence of retarded testicular growth after the age of 5, there appears to be no danger to fertility if both testes are out of the scrotum up to puberty In support of this observation are 14 men in my study who fathered children after bilateral retention which was not corrected, on one or both sides, until ages ranging from 8 to 18 years A fifteenth man had a son at age 41, when both his testes were out of the scrotum

Table 1 shows how the fertile testes of these men reached the scrotum, at what age, the probable reason for infertility of the mate in 3 men, and the number of children each man had at followup Only 2 of the 15 patients had had hormone

TABLE 1 *Scrotal route responsible for paternity in 15 men with bilateral undescended testes*

Route to Scrotum	Case	Levels of Arrest and Age Testes Reached Scrotum				No Children	Reason for Infertility of Mate
		Right		Left			
		Position*	Age	Positions	Age		
Bilateral spontaneous descent	1	External ring	9	Impalpable	9	1	
	2	Impalpable	10	Impalpable	10	3	
	3	External ring	12	External ring	10	4	
	4	External ring	12	Impalpable	12	2	
	5	External ring	12	Canal	18	3	
	6	Canal	13	Canal	15	2	
Unilateral spontaneous descent	7	Impalpable	11	—	—	3	Left canalicular testis removed at 23, before marriage
	8	Impalpable	14	—	—	8	Left agenesis Exploration at 14
Bilateral one stage orchiopexy	9†	Canal	10	Abdomen*	10	2	
	10	Canal	11	External ring	11	2	
	11	External ring	11	Canal	11	1	
	12†	External ring	12	External ring	12	3	
Unilateral one stage orchiopexy	13	External ring	8	—	—	4	Left testis descended from external ring at 21, atrophied
Spontaneous descent plus one stage orchiopexy	14	External ring Descended	8	Canal Orchiopexy	8	1	
Undescended when son born at age 41	15	Canal Orchiopexy	53	Abdomen* Orchiectomy	53	1	

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* Level of arrest was determined on clinical examination or at operation The 2 abdominal testes were not palpable clinically

† These 2 patients had 12,000 and 10,000 units chorionic gonadotrophin, respectively, prior to operation

therapy, 1 receiving 10,000 units and the other 12,000 units Each subsequently had bilateral orchiopexies, at ages 10 and 12

The value of doing orchiopexy during the first 5 years of life cannot be determined until studies of long term results are available for comparison with results following orchiopexy at later ages Excluding the testes that are intrinsically defective, in the light of our present knowledge it seems that more testes will be saved from irreparable damage if the physician will keep in mind the limits beyond which the testes must not be permitted to remain outside the scrotum and if he impresses on the parents the importance of treatment within that limit While puberty is still a safe age, treatment should be started well before that time

If the clinical findings do not demand operation earlier in the boy with bilaterally undescended testes, I prefer to give the hormone at about the age of 8 At this age retention *per se* has not yet caused irreparable damage to the testes, and if operation is necessary, the growth the child has attained by then facilitates the procedure The unilaterally undescended testis presents a less urgent problem from the standpoint of infertility, because its mate already in the scrotum is presumably normal But from the standpoints of cosmetic appearance, psychic trauma and possible development of malignancy, the unilaterally undescended testis should be accorded the same plan of treatment as that followed for bilaterally undescended testes

It is not known how much residence outside the scrotum contributes to development of malignancy in a testis Among 199 undescended testes I studied, there were 4 with seminoma After the study had been reported, a fifth seminoma was detected in a testis positioned by orchiopexy 6 years previously, when the patient was 39 years old At the same operation his opposite testis was removed because of a seminoma This case, among others in the literature, suggests that orchiopexy does not prevent malignancy But it should be noted the patient was 39 years old at the time of the operation

SUMMARY

The basic principles of orchiopexy are 1) dilatation of the scrotum for reception of the testis, 2) freeing the testicular vessels and freeing the vas sufficiently to position the testis without tension, 3) high ligation of the vaginal process, 4) use of some means of fixation and traction so that the testis will remain in the scrotum

Less manipulation is exerted on the testis and less tension is placed on its vascular supply in the one-stage orchiopexy than in the two-stage operation This minimizes the possibility of damage to the testis from operative trauma and makes the one-stage orchiopexy the preferable procedure

Hormone stimulation is a valuable diagnostic measure Its use prior to operation differentiates between the testis that will descend spontaneously and the one that must be explored It is of particular value when bilaterally retained testes are not palpable clinically

The amount of hormone given must be large enough to insure descent of the

testis in the absence of congenital anomalies of the testis, its vessels and mesentery and the structures composing its pathway of descent It is best administered at about the age of 8 This age allows for spontaneous descent well before retention in itself can cause irreparable damage to the testis, and if operation is necessary, it insures better developed tissues to work with than would be encountered in a younger child Operation must not be deferred beyond puberty, as established by the first pubic hair And the unilaterally undescended testis should be treated according to the plan followed for bilaterally undescended testes

There appears to be no danger to fertility if both testes are out of the scrotum up to puberty In a series recently reported, 14 men fathered children after bilateral retention which was not corrected on one or both sides before ages ranging from 8 to 18 years And a fifteenth man fathered a son at age 41, when neither testis was in the scrotum

Orchiopexy does not appear to prevent subsequent development of malignancy in the testis

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USE OF ANTEROPUBIC FASCIAL SLING FOR TREATMENT OF SURGICAL INCONTINENCE IN THE MALE

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This presentation will summarize my experience and thoughts pertaining to the fascial sling placed anterior to the pubis and about the bulbous urethra for the control of urinary incontinence Ten and one-half years have elapsed since the first case was operated upon A total of 8 cases form the basis of this report In 5 cases the aponeurosis of the rectus muscle was used, in 2 cases the fascia lata of the thigh was employed, while the eighth case was subjected to the use of both at different intervals of time The technique and results of these anteropubic fascial slings which compress the bulbous urethra have been presented before the Mid-Atlantic Section of the American Urological Association in 1955 and 1956 [1] [2] The results are not completely satisfactory

The incontinent patient as a rule is an unhappy, emotionally unstable individual He is more than willing to undergo any type of operation which will restore his urinary continence He should be apprised of the questionable results of all operations for urinary incontinence A sufficient interval of time must be allowed to pass to corroborate the fact that incontinence is to be permanent and irrevocable All pertinent studies must first be pursued and corrective surgery performed for any pathologic deviations found within the bladder and urethra which may have a causal relationship to the incontinent status

The medical literature is replete with numerous surgical and non-surgical techniques for correction of this distressing condition The principle of the fascial sling is not new and novel It has been tried in the past in both male and female with indifferent results Incontinence of neurologic origin will not be considered The sling operation, until additional study and results are reported, should be reserved for incontinence which follows operations on the obstructive prostate, or the incontinence which follows trauma to the urethra

It is difficult to collect a series of cases as incontinence is not commonly encountered Of the 8 cases reported from our clinic we were directly responsible for incontinence in 1 patient 80 years of age The remaining 7 patients were initially operated upon by others and were referred for corrective surgery

MATERIAL

Eight patients were operated upon between 1945 and 1956 and ranged in age from 23 to 80 years The precipitating cause of incontinence in 5 cases was transurethral prostatic resection, in 1 case perineal prostatectomy, in 1 case

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass , June 4-6, 1956

[1] Uhle, C A W The fascial sling An old surgical principle with a new concept in the correction of incontinence of urine in the male Presidential address, meeting Mid-Atlantic Sec , A U A April 15, 1955 To be published

[2] Uhle, C A W and Bradley, R H Jr The use of fascia lata strips in the sling operation for urinary incontinence in the male Meeting Mid-Atlantic Sec , A U A April 20, 1956 To be published

TABLE 1

Case	Age	Cause of Incontinence and Diagnosis	Sling Operation	Result
1	51	Perineal prostatectomy Benign prostate	Rectus fascia 1945	Partially satisfactory
2	67	Transurethral resection Carcinoma of prostate	Rectus fascia 1946	Partially satisfactory
3	23	Urethral trauma Multiple operations	Rectus fascia 1948	Partially satisfactory
4	65	Transurethral resection Benign prostate	Rectus fascia 1950	None
5	52	Transurethral resection Benign prostate	Rectus fascia 1951	None
6	80	Suprapubic prostatectomy Benign prostate with abscess	Fascia lata 1952	None
7	62	Transurethral resection Carcinoma of prostate	1 Rectus fascia 1955	None
			2 Fascia lata 1956	Poor but partially satisfactory
8	28	Transurethral resection Median bar	Fascia lata 1955	None

suprapubic prostatectomy Trauma to the urethra with multiple operations for correction and over-dilation with sounds were responsible for incontinence in 1 case, the youngest of the group The strips forming the sling were obtained from the rectus fascia in 6 cases Fascia lata strips were used in 3 cases in one of which rectus strips had been utilized unsuccessfully in an initial attempt to control incontinence The ages of the patients, causes of incontinence and diagnosis, type of sling operation and dates, and results are outlined in table 1

PHYSIOLOGIC CONCEPTS AND CRITIQUE

It was thought that the creation of an artificial sphincter about the bulbous urethra would aid in the control of urine in several ways 1) Tension of the abdominal wall would compress the sling against the bulbous urethra The sling would be particularly efficient in the erect posture of the patient or when intra-abdominal pressure was increased by coughing or sneezing 2) The perineal body containing the external sphincter mechanism would be elevated and strengthened Of interest in this respect is the recent observation of Beneventi and Marshall[3] "The external sphincter of continent men moved upwards and downwards for a surprisingly great distance (one inch, more or less) while the subject voluntarily started and stopped the stream " 3) Urinary flow would be decreased by compression of the bulbous area of the urethra against the urogenital diaphragm This would be comparable to the hinderance of the flow of water through a rubber hose which has been acutely angulated A similar effect can be obtained during the act of micturition if one pulls the suspensory ligament of the penis upwards The overall poor results in the cases reported may possibly be explained by the fact that these postulates have not been reproduced with the anteropubic course of the sling The sling may lack resilience, the anteropubic course may provide the wrong fulcrum, the connective tissue about the bulbous urethra may give and permit loosening of the sling, the perineal body may not be elevated

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[3] Beneventi F A and Marshall, V F Studies of urinary incontinence in men J Urol, 75 273–284, 1956

Lewis[4] has stated that urine is not normally held at the bulb of the urethra nor at the external sphincter but is held at the neck of the bladder His opinion is that it is more logical to direct the surgical approach to the neck of the bladder, and to use the same principle as in the Marshall-Marchetti operation for incontinence in women He has used this procedure twice in men after removal of all the prostatic tissue to allow angulation of the thinned tube at the vesical orifice He had complete success in one case, failure in the second Lewis[4] has remarked that the principle of a sling of fascia activated by striated musculature is completely erroneous No tendon sheath or pathway for free movement of the sling is provided and any muscle pull on the sling is nullified by scarring within a few days after surgery The sole action of the sling is elevation and kinking of the urethra

Strong and Van Buskirk[5] have described a satisfactory result in 1 case in which a rectus fascial sling was placed retropubically at the apex of the prostate through a perineal exposure

THREE IMPORTANT CONSIDERATIONS IN OPERATIVE TECHNIQUE

The operative technique of the fascial sling employing both the rectus fascia and fascia lata has been stressed in previous presentations [1] [2] In the most recent edition[6] of Dodson's UROLOGICAL SURGERY a section is devoted to the fascial sling

Attention should be directed to certain details of comparison between the rectus fascial sling and the fascia lata sling The rectus fascial sling (fig 1) is a time-consuming operation and large defects are left in the aponeurosis of the rectus abdominis These should be closed with wire to prevent subsequent weakening In excising a 1 cm strip of rectus fascia care should be exercised in not being too near the lateral margin of the rectus muscle where perforations of small branches of the tenth to twelfth intercostal nerves are found The strip is materially weakened if these are included, and will break when tension is applied This unfortunate accident occurred in two patients (cases 4 and 7) In contrast the fascia lata strip is easily and rapidly removed from the lateral aspect of the thigh, is very strong and does not break with tension (fig 2) It can be speedily placed in position

When tunnels have been formed by blunt dissection on either side of the root of the penile body in front of the symphysis, a sufficient thickness of fibroareolar tissue must be left attached over the bulb of the urethra (fig 3) When this bridge of perineal tissue is perforated to receive the fascial strips it should be of such strength and thickness that the sling will not be pulled distally and become

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[4] Lewis, L G Discussion of Uhle paper

[5] Strong, G H and Van Buskirk K E An operation for the cure of total urinary incontinence in the male Report of one case J Urol, 66 234–237, 1951

[6] Dodson, A I Urological Surgery St Louis C V Mosby

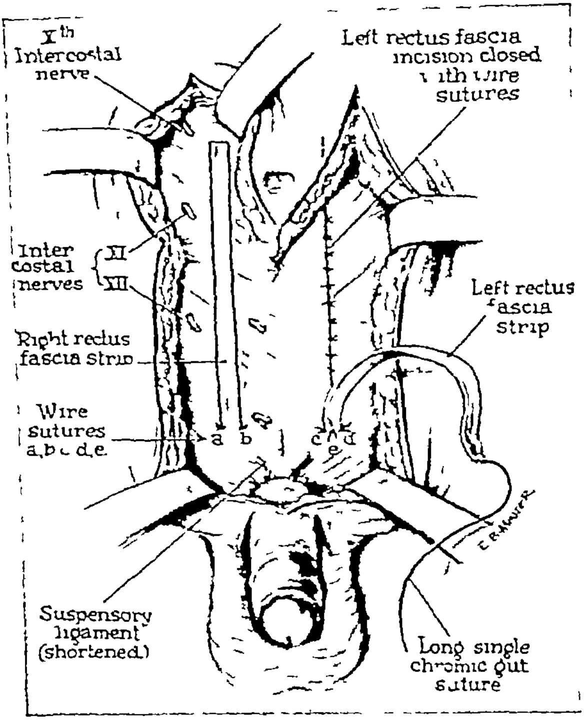
Xth Intercostal nerve
Left rectus fascia incision closed with wire sutures
Inter costal nerves
XI
XII
Left rectus fascia strip
Right rectus fascia strip
Wire sutures a, b, c, d, e.
a
b
c
d
e
Suspensory ligament (shortened)
Long single chromic gut suture
E. B. Minter

FIG 1 Straight single suprapubic incision is made in form of letter Y Preparation of rectus fascial strip Rectus aponeurosis closed with wire Suspensory ligament of penis has been shortened

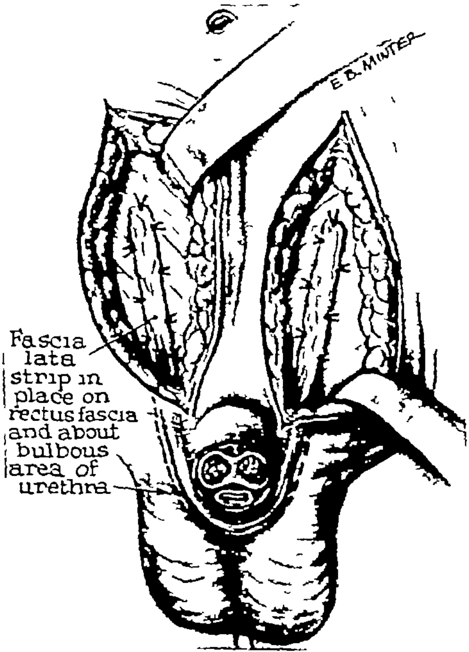
E. B. Minter
Fascia lata strip in place on rectus fascia and about bulbous area of urethra

FIG 2 Fascia lata sling attached to aponeurosis of rectus Fascial strip should be 11 to 12 inches in length and ¾ to 1 inch in breadth Combined perineal incision may be used to anchor it in place

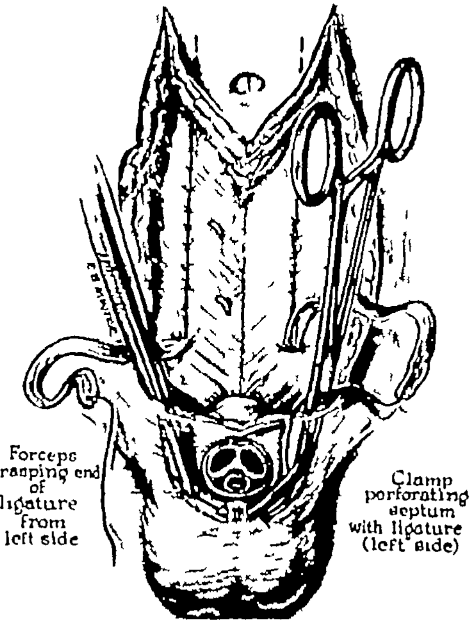
Forceps grasping end of ligature from left side
Clamp perforating septum with ligature (left side)

Fig 3

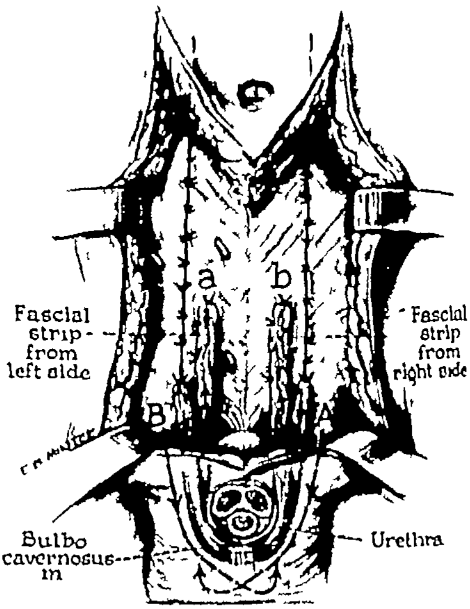

Fig 4

Fig 3 Introduction of fascial strips through bulbous area septum Before withdrawing clamp from septum, ligature attached to strip (right side) is introduced into jaws of clamp

Fig 4 Rectus fascial sling completed and strips sutured to rectus aponeurosis Amount of tension to be placed on these strips is dependent upon absence of urethral flow when assistant makes pressure upon previously filled bladder

ineffective when tension is placed on it (fig 4) The fascial strip may be secured in position through a combined perineal incision

The amount of tension or pull to apply to either type of sling can be grossly measured and is a most important part of the overall technique The bladder is filled to capacity with sterile water Pressure upon the bladder is made by an assistant Tension is made on the sling, and when water no longer can be forced through the urethra, the fascial strips are anchored in place by wire sutures

COMPLICATIONS

No serious postoperative complications have resulted in the group of 8 patients

In only one patient (case 1) a urinary fistula developed, which drained through the lower portion of the suprapubic incision It closed rapidly with catheter drainage

In a second patient (case 2) an indwelling urethral catheter was not employed postoperatively This error in judgment was followed by retention of urine In attempting to pass a catheter, the urethra was perforated In order to restore continuity the entire sling component was freed and then restored Following adequate catheter drainage no fistula developed

There have been no cases of urethral necrosis and sloughing with extravasa-

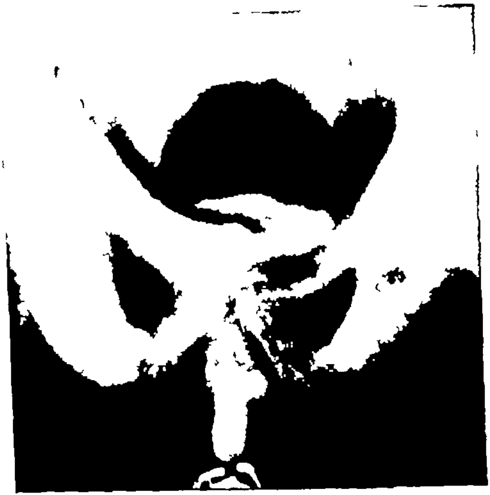

FIG 5 Case 2 Dilation of urethra proximal to sling Anteroposterior view

tion Cooney and Horton[7] reported one such complication twenty-four hours after removal of the indwelling catheter Campbell[8] has informed me that urethral sloughing occurred 1 year after a successful functional result in one of his cases

Pain in the groins, perineum and penis has not been a constant, long lasting complaint In some cases it has been severe in the immediate postoperative period and required much sedation Persistent cystitis, urethritis, edema of the penis and scrotum have been infrequent concomitants and of temporary duration

The most serious delayed complication is the development of a diverticulum in the urethra proximal to the sling In two of 3 patients (cases 1, 2, 3) with the most satisfactory results in the series of eight, outpouching and dilation of the urethra occurred (fig 5, case 2) Two patients referred to Lewis,[4] after failure of the sling operation, had diverticula In both these cases, the urethra was markedly dilated from the point of the obstructive sling to the bladder In spite of the damage to the urethra by obstruction they were totally incontinent If this complication should be a rather common finding in cases reported in the future the operation should be discontinued

RESULTS

The sling operation has been partially effective in 50 per cent of cases (cases 1, 2, 3, 7) These patients could stop and start the urinary stream at will, in the erect posture and void a variable quantity of ounces However, as soon as there was any stress or the patient did not have his mind on control, dribbling occurred Three of these patients (cases 1, 2 and 3) rated their dribbling as of minor consequence compared to their preoperative status Two patients (cases

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[7] Cooney, C J and Horton, G R An operation for the cure of urinary incontinence in the male J Urol, 66 586-592, 1951

[8] Campbell E W Personal communication

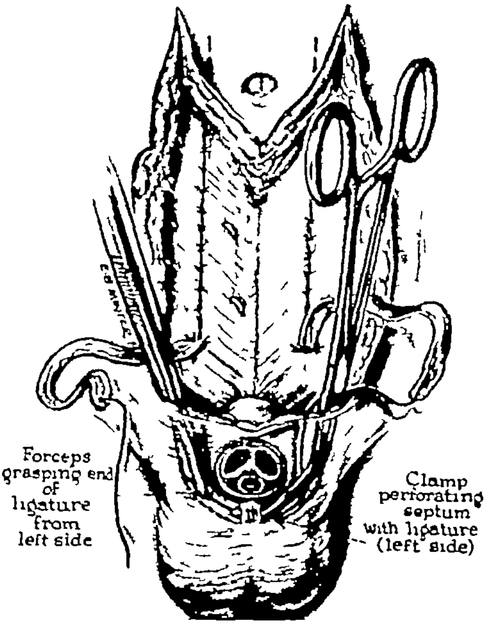
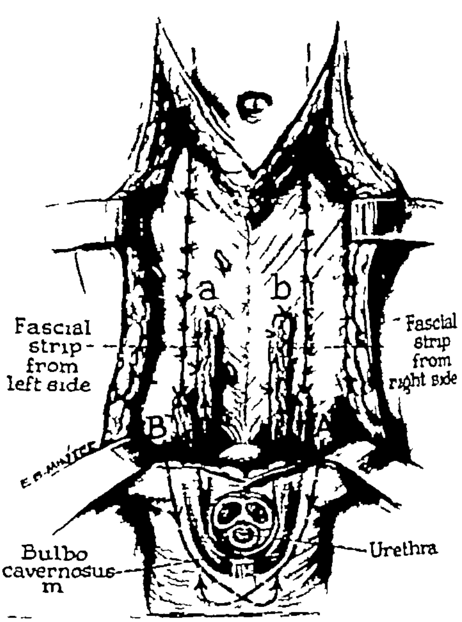

Forceps grasping end of ligature from left side
Clamp perforating septum with ligature (left side)

FIG 3



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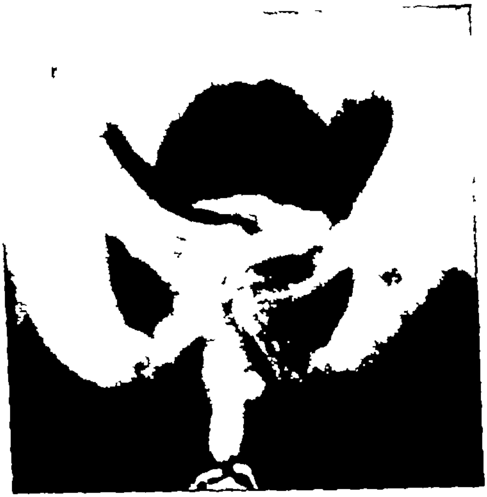

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[7] Cooney, C J and Horton, G R An operation for the cure of urinary incontinence in the male J Urol , 66 586–592, 1951

[8] Campbell E W Personal communication

1 and 3) had the sling shortened or reefed with beneficial but imperfect results while shortening of the sling in one patient (case 8) was valueless

Cooney and Horton[7] have reported good control in two of three patients Scott,[9] in his editorial notation in the YEARBOOK OF UROLOGY (1952) stated that he and his associates had performed the sling operation on 4 patients Control was judged good in two and considerably improved in two Lewis[4] operated upon one patient with no result Campbell[8] has reported good control in three patients after use of this procedure

According to Dodson,[6] Millin has employed the fascia lata sling placed anterior to the pubis with satisfactory results

In analyzing the results, individual or a combination of factors can be invoked to explain the overall poor results Technical reasons for failure would include operative errors in preparing the strips of fascia The strips may be too short for proper adjustment on the abdominal fascia, or they may tear during preparation It is difficult to improvise if this happens Failure is the end result An indwelling catheter should always be inserted at the conclusion of the operation An obvious cause of failure is insufficient tension of the sling upon the urethral component An explanation may be that, as time passes in the immediate postoperative period, the sling advances distal to the original site of adjustment because the fibrofatty areolar tissue, forming the septum over the bulbous end of the urethra, is not strong enough to maintain the sling in permanent position

SUMMARY

Eight patients were operated upon for incontinence of urine in whom a periurethral fascial sling coursing anterior to the symphysis pubis compressed and angulated the urethra Strips of fascia to form the sling were obtained from rectus aponeurosis and fascia lata of the thigh Results were partially effective in fifty per cent of cases A critique of the physiologic concept of the procedure, the comparative evaluations in the technique of the operation with its complications and the author's reasoning for failure of the operation have been presented

CONCLUSION

The validity and usefulness of a surgical technique for the correction of incontinence of urine depend upon the maintenance of principles of physiologic integrity The fascial sling as discussed in this paper is not basically physiologic It is the author's opinion that an additional period of study and analysis of cases on the part of numerous observers are indicated

404 Lankenau Medical Bldg , Philadelphia 31, Pa

[9] Scott, W W Editor's Insert Year Book of Urol Chicago Year Book Publishers 1952, p 251

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STEROID RESPONSE TO THERAPY IN PROSTATIC CANCER

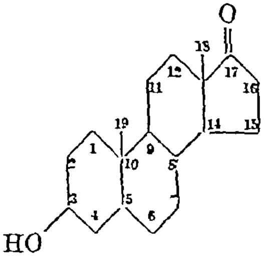
FREDERICK B BURT,*† ROY P FINNEY* and WILLIAM WALLACE SCOTT with technical assistance by Lawrason Perkins DeMuth and Joyce Eversole

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Md

Fifteen years have passed since Huggins and Hodges[1] first demonstrated the marked response of patients with widespread prostatic cancer to castration and estrogen therapy This response has now become thoroughly established Patients eventually relapse from this treatment and there is a growing body of evidence that this relapse is frequently associated with increased production of adrenal androgen It is now fairly well accepted that the object of therapy in cases of inoperable prostatic cancer is to lower the patient's androgen production Thus, tests measuring steroid metabolites may be an objective way of following a patient's response to therapy

The most widely used tests are based on the 17-ketone group of the steroid molecule which gives a specific color with meta-dinitrobenzene The large group of steroid metabolites which does not have a 17-ketone group has been studied much less intensely

The urinary 17-ketosteroids fall into two groups One group has no oxygen at position 11 These are called 17-keto-11 desoxysteroids



For clarity we shall refer to them as "androgen" metabolites in this paper Forty per cent of administered testosterone appears in the urine as one of these 17-keto-11-desoxysteroids[2] Precursors of these steroids are thought to be adrenal and testicular in origin

The other group has an oxygen at position 11 These are called 17-keto-11-oxysteroids We shall call this group "corticoid" metabolites

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Read at the annual meeting of the Section on Urology, American Medical Association, Chicago, Ill June 12-14, 1956

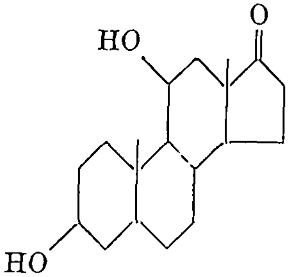
This work was supported in part by a research grant from the National Cancer Institute (C 2711 Endo), National Institutes of Health Department of Health Education, and Welfare and by an Institutional Grant (CT-805), to the Johns Hopkins University School of Medicine from the American Cancer Society

* Clinical Fellow American Cancer Society

† Supported by the Dodge Jones Foundation

[1] Huggins C and Hodges C V Cancer Res 1 293-297 1941

[2] Burt F B Finney R P and Scott, W W Unpublished data



in this paper These steroids are entirely adrenal in origin Six per cent of administered cortisone appears in the urine as one of these 17-keto-11-oxysteroids[2] Cortisone is never converted to an "androgen" metabolite nor is testosterone ever converted to a "corticoid" metabolite

The early workers in this field studied 17-ketosteroid excretion, a combination of "androgen" and "corticoid" metabolites In 1941 Satterthwaite[3] showed a decrease in total 17-ketosteroids following orchiectomy in 10 patients In 1942 Scott and Vermeulen[4] studied patients up to 8 months after castration They, too, noted a fall of total 17-ketosteroids This was followed by a rise to levels greater than the precastrate levels in 9 out of 10 patients In 1954 Birke, Franksson and Plantin[5] confirmed these findings They also showed lowering of "androgen" metabolites by estrogen and cortisone therapy

Many investigators have tried to demonstrate a characteristic steroid pattern or an abnormal steroid peculiar to untreated cancer patients However, no one has convincingly demonstrated any qualitative or quantitative differences in the 17-ketosteroid excretion between the normal and cancerous patient

Recently, refined methods have been developed which permit quantitative separation of individual steroid metabolites in unaltered form We felt that further study of the therapeutic response and ultimate relapse of patients with prostatic cancer, using such methods, would be profitable Such a refined method requires the use of the enzyme glucuronidase This preparation was unavailable to the previously mentioned investigators It is necessary for the quantitative hydrolysis of "corticoid" metabolites which are conjugated with glucuronic acid in the urine [6] Previously used methods of strong acid hydrolysis cause chemical alteration of the "corticoid" metabolites [7]

METHODS

The methods we use are those of Dobriner and Gallagher [8] [9] [10] We collect urine for 3 days on hospitalized patients and incubate this with β-glucuronidase* for 5 days at pH 4.7. The urine is adjusted to pH 1 and extracted continuously with ether for 48 hours. The ether extract is washed with 2 N NaOH. This crude neutral extract is then subjected to a Girard reaction,[11] then a digitonin reaction[12] giving an α-ketonic fraction. The steroids are separated by chromatography on a silica gel column. The fractions thus obtained are identified by infrared spectrophotometry. Two "androgen" metabolites androsterone and etiocholanolone, and three "corticoid" metabolites, 11-hydroxyandrosterone, 11-hydroxyetiocholanolone and 11-keto-etiocholanolone, are isolated. For simplicity's sake, we have combined the individual values of the two "androgen" metabolites and also the three "corticoid" metabolites. The 17-ketosteroids are measured by a modified Zimmerman reaction.[13]

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[3] Satterthwaite, R W , Hill, J H and Packard, E F J Urol , **46** 1149–1153, 1941

[4] Scott, W W and Vermeulen, C J Clin Endocrinol , **2** 450–456, 1942

[5] Birke, G , Franksson, C and Plantin, L O (a) Acta Endocrinol Suppl 17, 1954, (b) Acta Chir Scand , **109** 1 and 129, 1955

[6] Gallagher, T F et al Recent Progress in Hormone Research, **9** 411–433 1954

[7] Lieberman, S , Mond, B and Smyles, E *Recent Progress in Hormone Research*, **9** 113–129, 1954

[8] Dobriner, K , Kappas, A , Rhoads, C P and Gallagher, T F *J Clin Invest* , **32** 940–949, 1954

[9] Lieberman, S and Dobriner, K Recent Progress in Hormone Research **3** 71–101, 1948

[10] Gallagher, T F Personal communication

RESULTS

Others have shown that structurally dissimilar steroids often yield the same urinary metabolites. It is important to note that when such steroids are administered to the same individual, the ratio of their metabolites is frequently quite different.[14] It is often conjectured that so-called "adrenal androgen" may be structurally quite different from testicular androgen. If such were the case one might expect considerable alteration of "androgen" metabolites depending upon their source, showing one ratio when chiefly adrenal, another when chiefly testicular in origin. However, the ratio of the "androgen" metabolites isolated during our investigation remained remarkably constant before and after castration or stimulation by ACTH or gonadotrophin. Administered testosterone did not alter this ratio. This suggests a structural similarity in testicular and adrenal androgen and testosterone.

Six patients were studied in respect to castration alone. Five patients had a prompt fall in their "androgen" metabolites and a good immediate clinical response. These results are shown in table 1.

Three of these 6 patients have been followed for six months or longer with no other therapy (fig. 1). Unfortunately two of these patients were placed on 3 mg. stilbestrol daily 7½ months (J.E. 60 CM) and 6 months (J.R. 61 CM) after castration when there was no evidence of clinical or chemical relapse. These 2 patients are still doing well, 16 months after castration. The first patient (top of figure) relapsed clinically at 6 weeks after orchiectomy and died of cancer 10 months postoperatively. The progressive rise of corticoid metabolites and the somewhat lesser rise of "androgen" metabolites paralleled his downhill course. This rise prompted an investigation of pituitary-adrenal relationships involved.

We wondered what pituitary hormones might be involved in the "corticoid" and "androgen" metabolite rise in our relapsing patient. Test doses of gonadotrophin and ACTH were given before and after castration.

Gonadotrophin caused a marked increase in "androgen" metabolites prior to

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* The β-glucuronidase (Ketodase$^{\text{T}}$) was generously supplied by Warner-Chilcott Laboratories, Morris Plains, N. J.

[11] Girard, A. and Sandulesco, G. Helv. chim. acta, 19: 1095, 1936.

[12] Butler, G. C. and Marrian, G. F. J. Biol. Chem. 124: 237, 1938.

[13] Callow, N. H., Callow, P. K. and Emmens, C. W. Biochem. J. 32: 1312, 1938.

[14] Dorfman, R. I. Recent Progress in Hormone Research, 9: 5-24, 1954.

TABLE 1 *Early response to castration*

Patient	Precastration androgen metabolites	Postcastration 3 weeks androgen metabolites	% Reduction in androgen metabolites	Clinical response at 3 weeks
R D 56 W M	5 85	1 77	70%	good
J E 60 C M	6 00	2 14	65%	good
W J 70 C M	2 71	1 24	54%	good
J R 61 C.M	4 58	2 51	48%	good
A S 70 C M	0 91	0 50	45%	fair
F J 60 C M	3 32	3 29	1%	none

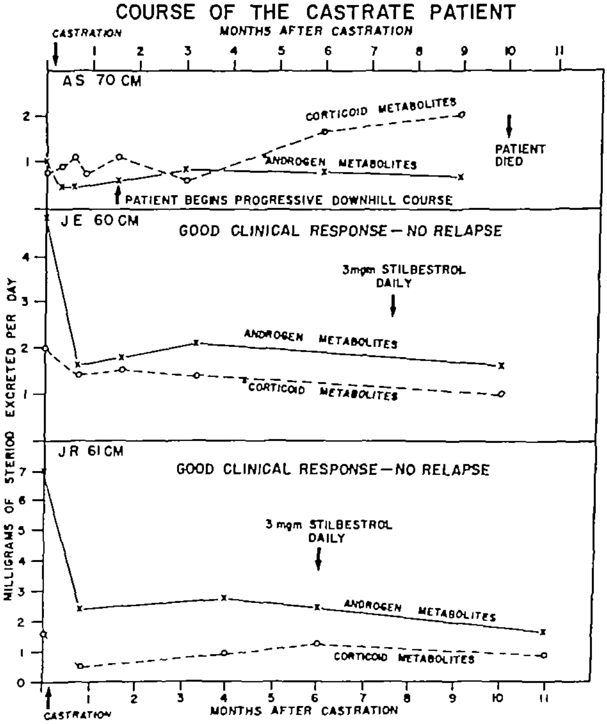


FIG 1 Urinary "androgen" and "corticoid" metabolites following castration (and estrogen administration)

castration (table 2) No rise or fall in "androgen" metabolites occurred after castration The "corticoid" metabolites remained unchanged It was concluded that gonadotrophin probably played no rôle in the rising steroids of the relapsing castrate patient

Two patients were tested with ACTH in similar manner In both, the response to ACTH was poor prior to castration (table 3) After castration the ACTH response was marked This suggests that adrenal response to ACTH is enhanced by orchiectomy This may explain the rapid relapse of some patients following a good response to castration

A vicious cycle, as shown above, fits many of the facts now known However, some uncertainty is present as to whether the stress caused by cancer activity is adequate to stimulate ACTH If this is true, a nonspecific stress could start the patient on a downhill course It is interesting to note that administration of stilbestrol did not interfere with the adrenal response to ACTH although it did

TABLE 2 *Loss of effectiveness of gonadotrophin (2500 units daily) following castration*

J.R. 61 C.M.	"Androgen" metabolites			"Corticoid" metabolites
	control	gonadotropin	% increase	
Precastration	4 58	8 75	−91%	Average increase 3 9%
3 weeks postcastration	2 51	2 17	−13 5%	
4 months postcastration	3 37	3 68	−9 2%	

TABLE 3 *Enhancement of ACTH response by castration (dose = 80 units ACTH I.M daily)*

J.E. 60 C.M.	"Androgen" metabolites			"Corticoid" metabolites		
	control	ACTH	% control	control	ACTH	% control
Precastration	6 00	5 43	−9 5%	2 98	3 62	−21 4%
3½ months postcastration	2 59	4 75	−83 5%	1 51	3 95	−95 5%
10½ months postcastration on 3 mg stilbestrol daily for 3 months	1 71	4 76	−178%	0 70	3 86	−308%
W J [illegible] C.M.						
Precastration	2 71	3 23	−19 1%	1 75	1 67	−4 5%
1½ months postcastration	1 34	4 11	−207%	0 84	1 66	−90 5%

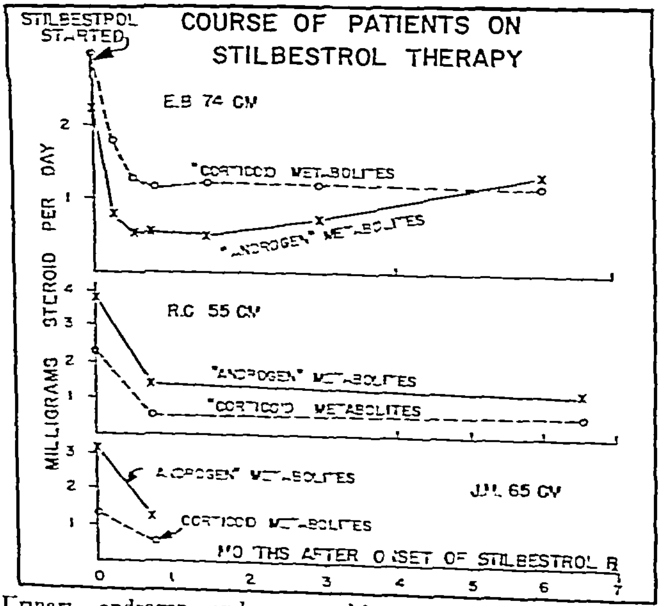
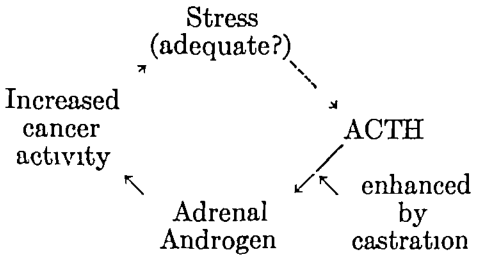


FIG 2 Urinary "androgen" and "corticoid" metabolites on stilbestrol therapy, 3 mg per day

lower "androgen" and "corticoid" metabolite levels This is good evidence that the adrenal inhibition by stilbestrol is mediated through the pituitary



Three non-castrate patients were followed while on 3 mg stilbestrol daily A dramatic fall in both "corticoid" and "androgen" metabolites is observed (fig 2) This would suggest pituitary inhibition of gonadotrophin and ACTH

TABLE 4 *Influence of stilbestrol on castrate patients*

Patient	' Androgen" metabolites			Corticoid" metabolites			Duration of estrogen therapy months
	control	estrogen	% decrease	control	estrogen	% decrease	
R D 56 W M	1 77	0 97	45%	1 53	0 63	59%	1
J R 61 C M	3 03	2 30	24%	1 44	1 00	31%	4½
F J 60 C M	3 19	2 21	31%	1 13	1 01	11%	2
J E 60 C M	2 59	1 71	34%	1 51	0 80	47%	3

TABLE 5 *Response to cortisone by a castrate patient, F P 56 C M on stilbestrol*

' Androgen" metabolites			Corticoid" metabolites		
control	cortisone	% change	control	cortisone	% change
3 8	0 22	−94 2%	1 00	9 91	+891%

Cortisone dose—100 mg daily
Immediate clinical response—good

TABLE 6 *Correlation between tendency to relapse and ratio of urinary androsterone etiocholanolone*

Patient	Ratio androsterone etiocholanolone	Therapy			Months followed	Present state
		castrate	estrogen	cortisone		
F P 56 C M	0 87	X	X	X	17	relapse
R D 56 W M	0 82	X	X	X	16	dead
A S 70 C M	0 81	X			10	dead
F J 60 C M	0 69	X	X		6	relapse
R C 55 C M	0 54		X		7	well
J M 65 C M	0 52		X		6	well
J E 60 C M	0 51	X	X*		15	well
J R 61 C M	0 38	X	X*		14	well
W J 70 C M	0 34	X			6	well
E B 74 C M	0 25		X		7	no relapse

* Given without indication

Four castrate patients were placed on 3 mg stilbestrol daily from one to seven and one-half months after orchiectomy All showed lowering of "corticoid" and "androgen" metabolites (table 4)

One patient who relapsed from stilbestrol and castration showed a dramatic fall of "androgen" metabolites on 100 mg cortisone (table 5) Of course, his "corticoid" metabolites rose This patient showed dramatic relief of symptoms on 100 mg of cortisone On 50 mg his symptoms returned This treatment was repeated three times with the same clinical results

Ten patients have been followed closely They fall into two clinical groups regardless of therapy those who have done well, and those who have not

Two "androgen" metabolites, androsterone and etiocholanolone, are routinely isolated The patients who did poorly and relapsed produced a higher percentage of androgenic androsterone in relation to physiologically neutral etiocholanolone

Table 6 shows the patients listed according to the ratio of the two "androgen" metabolites The first four have done poorly despite various types of therapy The second six have done well with a single therapeutic measure

SUMMARY

"Androgen" metabolites fall after castration

"Corticoid" and "androgen" metabolites may rise when a patient relapses

Gonadotrophin has no effect on steroid levels on the castrate patient

The effect of ACTH on both "androgen" and "corticoid" metabolites is markedly enhanced by castration

Stilbestrol causes a fall in "androgen" and "corticoid" metabolites in the intact and castrate patient

Cortisone can effectively eliminate "androgen" metabolites

The tendency to relapse from therapy may be associated with the degree of conversion of certain precursors, such as testosterone, to androgenic androsterone rather than physiologically inactive etiocholanolone

In our limited series, the clinical state has invariably paralleled the chemical state

The authors gratefully acknowledge the technical assistance of Josephine Carson Miller and Elizabeth Barnhardt

We wish to thank Dr T F Gallagher for his kindness in showing us the methods in use at Sloan-Kettering Institute in February 1954

We wish to thank Dr Charles Tesar, of the Brady Research Laboratory, for advice and assistance throughout this project

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PERINEAL SURGERY FOR CARCINOMA OF THE PROSTATE WITH FOLLOWUP DATA TO TEN YEARS

DANIEL R HIGBEE

This group of 49 cases of operable carcinoma of the prostate was treated by perineal surgical removal between 1944 and early 1955 The group represents 22 per cent of the cases of carcinoma of the prostate treated during this period They have been divided into two groups based on the extent of involvement at the time of the surgery as shown by the histological examination of the tissue removed

In group 1 radical perineal surgical removal only was employed in 38 cases (table 1) In these 38 cases pathological examination of the prostate and vesicles showed the malignancy to have been confined to the prostate or to have extended somewhat into the capsule but not to the seminal vesicles Four of these later required orchiectomy because of a local recurrence of malignancy

In 11 cases histological examination showed the malignancy to have involved the prostate with extension to one or both vesicles, although clinically this extension had not been evident before surgery These were treated by perineal surgical removal followed by bilateral orchiectomy as soon as the pathological extension was proved These 11 cases comprise group 2 (table 2) These two main groups form the body of this discussion

However, two additional groups of cases are included since both have a bearing on the problems associated with perineal biopsy Ten cases were treated by perineal enucleation followed by orchiectomy (table 3) and 11 cases were treated by radical perineal removal in which no evidence of carcinoma was found (table 4)

The operative mortality rate for the 49 cases was 4 per cent One death occurred on the fifth postoperative day from a large pulmonary embolus, the other death came the day of surgery from a coronary thrombosis

The overall morbidity rate was comparatively low, however, 5 complications were pulmonary in character All five were believed to be due to small emboli with or without accompanying evidence of pneumonia There was one case of thrombophlebitis of one lower extremity

Of the other actual or potential complications there were two rectal injuries which were repaired at the time of surgery, and which healed by primary union

Some degree of lack of urinary control was present in 55 per cent of the cases immediately following surgery, and persisted for varying periods of time One patient was still totally incontinent after 3 months at the time of his accidental death, one is slightly incontinent when he wears an abdominal belt, but is continent without it, eight were totally incontinent for from 2 to 3 months, but each eventually regained satisfactory urinary control In 1 patient a vesical neck stricture developed due to a recurrence of malignancy and he requires an occasional urethral dilatation

Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass June 4-6, 1956

The worth of surgical removal for prostatic carcinoma either alone or in conjunction with palliative measures such as orchiectomy, estrogen therapy or radiation therapy can be established only by followup data extending over years of time. In this group of cases, one patient with a moderate-sized local lesion, treated by radical removal only, showed no evidence of local recurrence for 7 years but eventually died of metastases. At the other extreme, one individual who had involvement of the prostate and both vesicles at the time of his surgery, which included orchiectomy, lived comfortably for 10 years and suddenly died of coronary occlusion. These are, of course, extreme illustrations. However they point up the difficulty of attempting to draw conclusions from a relatively small group of cases.

Of the 38 cases, comprising group 1, treated only by radical perineal prostatectomy two were operative deaths, and three are dead from causes other than

TABLE 1. *Radical perineal prostatectomy carcinoma confined to prostate histologically, 38 cases*

Operative mortality	2	5.2%
Died of causes other than ca 4 mos 2½ yrs and 3 yrs	3	8.0%
Remaining 33 cases		
5 yrs or over—17 cases		
Recurrence of ca		
Dead 5 and 8 yrs	2	5.2%
Alive 3–6 yrs 1–5 yrs	4	10.4%
Free of recurrence and alive	11	29.0%
1 to 5 years—16 cases		
Recurrence of ca		
Dead none	0	
Alive 1–4 yrs	1	2.6%
Free of recurrence and alive	15	39.5%

TABLE 2. *Carcinoma of prostate with extension to vesicles histologically, radical perineal with orchiectomy*

Year	Age	Active years	Length of life	Cause of death	Postmortem
1945 (DA)	69	10	10	Coronary (1 day)	No
1945 (DB)	69	8	9	Ca of prostate	Yes
1946 (AC)	64	4	5	Ca of colon	No
1946 (JQ)	58	4	6	Ca of prostate	No
1949 (WC)	72	7	Alive		
1952 (LK)	63	4	Alive		
1953 (BW)	58	3	Alive		
1953 (AM)	68	3	Alive		
1953 (EB)	74	1	2	Esophageal hem	Yes
1953 (EK)	78	3	Alive		
1954 (CF)	72	2	Alive		

TABLE 3 *Carcinoma of prostate conservative perineal prostatectomy with orchiectomy, 10 cases*

	Length of life	Cause of death	
Died of ca of pros —3			
1945 (JB) 73	2½ yrs	Recurrence—diabetes	Known ca
1948 (JP) 73	6 yrs	Recurrence	Unsuspected
1946 (WB) 76	2½ yrs	Recurrence	Known ca
Died of other causes—3			
1946 (GS) 70	5 yrs	Broken shoulder	Unsuspected
1949 (RK) 73	5 yrs	Cardiac decomp	Unsuspected
1948 (RC) 63	2 mos	Cardiac infarct	Unsuspected
Alive with ev of recurrence—1			
1954 (A) 74	Alive 1 yr		
Alive without ev of recurrence—3			
1946 (CM) 66	Alive 8 yrs		Biopsy neg
1949 (AT) 77	Alive 7 yrs		Unsuspected
1952 (HB) 69	Alive 4 yrs		Biopsy pos

TABLE 4 *Radical perineal prostatectomy no evidence of carcinoma histologically, 11 cases*

Age	Year	Clinical	Histological diagnosis	Present status
67 (JE)	1945	Very hard gland	Hyper + chr pros	Died 1951—6 yrs
72 (R)	1949	Hard nodule	Hyper + fibrosis	Alive 1956—6 yrs
76 (H)	1949	Very hard gland	Hyper + fibrosis	Alive 1953
55 (T)	1950	Hard right lobe	Hyperplasia	Alive 1956—6 yrs
63 (McD)	1950	Hard right lobe	Hyper + chr pros	Alive 1955—6 yrs
52 (F)	1951	Hard prostate	Granuloma	Alive 1956—5 yrs
68 (H)	1952	Hard prostate	Fibro adenoma	Alive 1953
62 (CS)	1952	Hard nodule	Adenoma	Alive 1956—4 yrs
73 (D)	1954	Hard prostate	Hyper + chr pros	Operative mortality 9th PO day
66 (T)	1955	Hard left lobe	Chr pros	Alive 1956
67 (Z)	1955	Very hard gland	Hyper + chr pros	Operative mortality 6 wks PO

prostatic malignancy (lobar pneumonia 2½ years, accidental death 4 months postoperatively, and one cardiac death after 3 years)

Of the remaining 33 cases, one is alive and free of recurrence at the end of 10 years, one is dead of recurrent carcinoma of the prostate after 8 years, two are alive and well after 7 years, six are alive 6 years after surgery (three of these showing evidence of local recurrence), five are alive after 5 years and one died of carcinoma of the prostate 5 years after surgery, five are alive after 4 years, one after 3 years, seven after 2 years, and three after 1 year In other words, of the 17 cases with 5–10 year followup data none died in less than 5 years' time Two died of malignancy subsequently, four have recurrences, and 11 are alive and well Of the 16 with 1–5 year followup data there is one local recurrence after 4 years

In group 2, the 11 cases treated by radical perineal prostatectomy, orchiectomy and estrogen therapy, which at the time of surgery showed extension to one or both vesicles, two have died of recurrent carcinoma of the prostate in 9 and 6 years respectively, and three died of other causes (one of coronary thrombosis after 10 years, one of carcinoma of the colon after 5 years, and one of esophageal hemorrhage after 2 years) Of the remaining 6 cases, one is alive after 7 years without evidence of recurrence, one after 4 years, three after 3 years (one of these with a question of local recurrence), and one after 2 years

Again in group 2 none have died in less than 5 years of recurrence of prostatic malignancy

In summing up the 22 cases with 5–10 year data, none have died of a recurrence in less than 5 years Fourteen (or 63 per cent) continue to be alive and well for longer varying periods of time

This discussion would not be complete without the presentation of two other groups of cases One group includes 10 cases in which enucleation and orchiectomy were accomplished They are the ones misdiagnosed preoperatively as benign lesions, and elderly individuals with large adenomatous glands known to have some malignant involvement at the time of surgery but who, due to age or physical condition, required conservative treatment Of these 10 cases, three died of carcinoma of the prostate 2 and 6 years after treatment, three died of other causes (one in 3 months and two 5 years after surgery), one is alive with evidence of recurrence 1 year after surgery, and three are alive without evidence of recurrence 4, 7 and 8 years respectively

The final group of 11 cases was treated by radical perineal prostatectomy, but on histological examination the glands showed no evidence of malignancy One of these was a prostatic granuloma with giant cell formation, two adenomatous hyperplasia, three hyperplasia with fibrosis, and five chronic prostatitis Of this group 2 patients with chronic prostatitis died following surgery (one on the ninth postoperative day and one 6 weeks postoperatively) both of infectious pulmonary complications Of the other nine, one died 6 years after surgery, two were lost track of after 4 years and 1 year respectively, and of the remainder three are alive and well after 6 years, one after 5 years, one after 4 years, and one after 1 year Perineal biopsy was employed in several of the above cases

The value of examining a frozen section of tissue at the time of surgery has fluctuated with me, since accurate diagnosis with polychrome methylene blue is difficult at best, and the surer H and E technique has not been employed until recently Also I am not sure that biopsy *per se* does not carry some risk of spreading malignancy in the prostatic area In 3 instances the frozen section was interpreted to be free of carcinoma only to have the report on the permanent sections run on the same tissue returned positive 5 days later In two of these patients a radical operation was performed immediately

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In 2 cases there was no evidence of malignancy in the frozen section and none in the permanent sections, but carcinoma was found elsewhere in both glands upon removal

Transurethral prostatic resection established the diagnosis of prostatic malignancy in 3 cases In two of these, the diagnosis was confirmed when the glands were completely removed, and in the third there was no evidence of malignancy in the remaining glandular tissue

As a result of these experiences, I accept the frozen section diagnosis when positive, but follow the practice of removing the prostate when an indefinite frozen section diagnosis is received, provided the clinical evidence strongly suggests the presence of malignancy In some instances it has been advisable to obtain a perineal biopsy specimen and to defer further treatment until a report by standard staining methods is obtained

In conclusion, the results of surgery on 49 patients with carcinoma of the prostate treated by radical perineal prostatectomy show that the outcome of this type of surgery has been comparatively favorable

In addition, two groups of cases, one with malignancy treated conservatively and one without malignancy, but treated by radical surgery, have been reviewed In the last group, two operative deaths in patients with severe prostatitis but without histological evidence of malignancy suggest the desirability of avoiding extensive surgery where severe chronic infection is present

While biopsy never will be completely reliable in the detection of prostatic carcinoma, its wider use in routine perineal surgery together with yearly prostatic examinations should further minimize errors in diagnosis and increase the percentage of malignant glands found early enough to warrant complete surgical removal

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FURTHER EXPERIENCES IN TREATMENT OF CARCINOMA OF PROSTATE WITH RADIOACTIVE CHROMIC PHOSPHATE AND YTTRIUM CHLORIDE

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From the Urological Section of the Surgical Service of Chicago Wesley Memorial Hospital, and the Radio Isotope Unit, Veterans Administration Research Hospital and the Departments of Urology and Biochemistry, Northwestern University Medical School, Chicago, Ill

The treatment of prostatic carcinoma by means of interstitial irradiation with radioactive gold (Au 198), chromic phosphate (P_{32}) and yttrium chloride (Yt 90) has been carried out by several groups over the past three years Our experiences with these substances have recently been brought up to date and published[1] The results have been somewhat less than originally hoped for, but are sufficiently encouraging in some cases to make us believe that the method has some value in the control of this usually fatal disease Further experiences following the use of radioactive yttrium chloride and chromic phosphate have prompted this report

The selection of patients and method of injection have been described elsewhere[1] The additional patients reported here were all injected by means of multiple needles introduced through the perineum, guided by a finger in the rectum We have continued to utilize this method because we feel that distribution is equal to that obtained by the retropubic route and that we are better able to protect the rectum while placing the needles In addition, the perineal procedure carries little morbidity and the hospital stay is usually quite brief

The series of patients receiving radioactive yttrium chloride now totals 12 and the results are summarized in table 1

It is evident from table 1 that only 2 patients out of the total group of 12 have received any clinical benefit from the yttrium injection Seven of this group have had post-injection perineal biopsy performed and six of these biopsies showed active adenocarcinoma One patient was injected 3 times and biopsy material obtained 3 months following each injection remained positive Two patients were injected twice and both had positive biopsies after the second injection None of this group of patients had received either estrogens or orchiectomy, although those showing progression of disease in spite of interstitial irradiation have recently been placed on estrogen therapy One patient of this group has had three negative needle biopsies at 3-month intervals and continues to do well

Dosages of radio-yttrium have ranged from 19 5 mc to 40 mc , depending on the size of the tumor There were no complications noted in any of these patients

Experimentally, we felt that radioactive yttrium offered promise in the

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass June 4-6, 1956

This work was made possible in part by funds from the Urological Research Fund of Chicago Wesley Memorial Hospital

* Markle Scholar in Medical Science

[1] Bulkley, G J Cooper, J A D and O'Conor, V J Treatment of carcinoma of the prostate with radioactive material J Urol , 76 837-845, 1956

TABLE 1 *Yttrium (Yt 90), 12 patients*

	Cases
Died of disease	2
Living with no change rectally	8
Living with gland softer and smaller	2

TABLE 2 *Chromic phosphate (P 32), 5 patients*

	Cases
Died of disease and bone marrow depression	2
Living without clinical improvement	3

control of prostatic carcinoma, chiefly because of its high energy beta rays and rapid fixation to tissue Clinically, this does not seem to be the case Urinary loss and loss into the bloodstream have been equal to that experienced with gold and chromic phosphate, so that the dose remaining in the prostate is probably quite a small percentage of the total injected dose Although this series of patients *is too small to be statistically significant, it seems to indicate* that radio-yttrium has no advantage over radio-gold in our experience Since radioactive gold has the added possibility of greater penetration due to the gamma ray component and is so much easier to produce and obtain commercially, it seems doubtful that radioactive yttrium will be widely used

The series of patients with prostatic carcinoma receiving radioactive chromic phosphate is summarized in table 2

None of the patients who received chromic phosphate apparently benefited from the *injection* There have been rather alarming complications in four patients of this group, apparently due to radiation damage to bone marrow These case reports are presented below in detail

CASE REPORTS

Case 1 See figure 1 A E was admitted to the hospital on March 17, 1955 with complaints of urinary difficulty Past history revealed a previous transurethral prostatic resection at another hospital in 1954 No pathological diagnosis of this tissue could be obtained Examination on entry revealed a hard, nodular, fixed prostate which proved to be adenocarcinoma on perineal needle biopsy Initial laboratory studies hemoglobin 12 9 gm , white blood cell count 5,700, with normal differential, blood urea nitrogen 7 9 mg per cent, and acid phosphatase, 0 28 Bodansky units X-rays showed no signs of bony metastases

On April 4, 1955, perineal injection of 21 5 mc radioactive chromic phosphate was accomplished with four No 22 gauge needles introduced perineally, and the Flocks' syringe The hemoglobin was 11 9 gm and white blood cell count 4,800 a week after injection

The patient was re-admitted August 15, 1955 for followup biopsy which was done on August 17, 1955 and was positive for active adenocarcinoma Laboratory studies hemoglobin 12 6 gm , hematocrit, 37 per cent, white blood cell count 4,300, with normal differential, blood urea nitrogen, 14 1 mg per cent, and

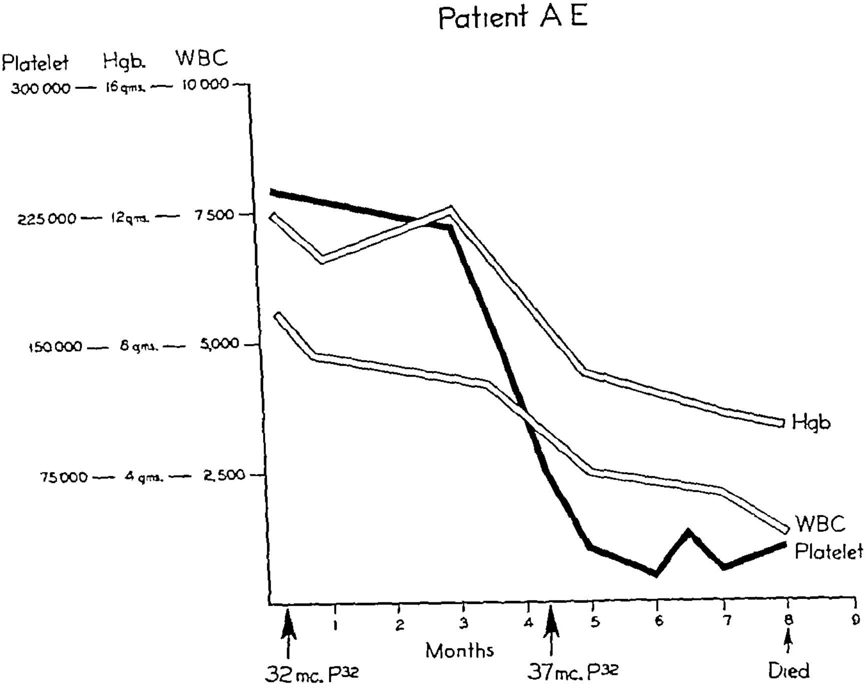

FIG 1

acid phosphate, 0 2 Bodansky units On August 24, 1955, 38 mc of radioactive chromic phosphate was injected perineally using 4 needles and the same technique as previously described

The patient was re-admitted on September 29, 1955 complaining of shortness of breath, swelling of the abdomen and severe epistaxis Examination revealed a hard, flat prostate and a liver enlarged to three fingerbreadths beneath the costal margin Admission white blood cell count was 2,500, hemoglobin 7 gm , hematocrit 27 per cent, bleeding time, 1 minute, coagulation time, 9 minutes, prothrombin time, 100 per cent, blood urea nitrogen, 15 4 mg per cent, acid phosphatase, 0 03 units, platelet count 16,000 Bone marrow aspiration revealed hypoplastic marrow with depression of all elements and no sign of metastatic carcinoma The platelet count rose to 104,000 under treatment and fell to 32,000 The blood urea nitrogen rose steadily over a 3-month period to 38 mg per cent and the acid phosphatase to 19 2 units The white blood cell count rose to 5,000 under treatment and later fell again A second perineal biopsy on November 30, 1955 showed adenocarcinoma The patient became progressively worse and died on December 28, 1955 Autopsy showed that death was due to a combination of pancytopenia from depression of bone marrow, arteriosclerotic heart disease and carcinoma of the prostate with some bony metastases which were not thought to be extensive enough in themselves to cause death The pathologist felt that bone marrow depression, probably from radiation damage, significantly contributed to the fatal outcome

Case 2 I K was admitted on January 10, 1955 with a complaint of difficulty in voiding and was found to have large residual urine. Rectally, the prostate was enlarged, hard, nodular and fixed. Perineal biopsy showed adenocarcinoma of the prostate. Laboratory studies: hemoglobin 13.7 gm., white blood cell count 6,100, hematocrit, 46 per cent, acid phosphatase, 0.64 Bodansky units, blood urea nitrogen, 24.5 mg. per cent. On January 17, 1955, 28.6 mc. of radioactive chromic phosphate was injected perineally using five No. 22 gauge needles and the Flocks' syringe. On February 14, 1955, a transurethral prostatic resection was done, sections of tissue removed showed adenocarcinoma with some areas of necrosis and inflammatory reaction from the radioactive material.

The patient was re-admitted on May 19, 1955 and rectal examination showed little change from the previous findings. Laboratory studies were not significantly changed except that the white blood cell count was 4,500. Perineal biopsy showed active adenocarcinoma and 75 mc. of radioactive gold was injected perineally.

He was re-admitted on December 1, 1955 for eye surgery. A second perineal biopsy showed active adenocarcinoma. Bone marrow puncture showed no tumor cells and no pathologic diagnosis was made. We have no evidence that there was any significant radiation damage to the bone marrow in this patient. There was very little change in the prostatic carcinoma rectally after two injections of radioactive material.

Case 3. W. S. had had a diagnosis of carcinoma of the prostate made in 1951 following a transurethral resection of the prostate. He was placed on estrogens by mouth for 3 years and in 1954 a bilateral orchiectomy was done. On admission to the hospital on June 2, 1955 he complained of back pain. Rectal examination showed an enlarged, hard, nodular prostate gland. Laboratory studies: white blood cell count 6,200, normal differential, acid phosphatase, 0.3 Bodansky units, hematocrit 45 per cent, blood urea nitrogen 9.3 mg. per cent. X-ray of the pelvis showed metastatic lesions. Perineal needle biopsy was negative but, because of the previous diagnosis and findings of metastatic carcinoma, a perineal injection of 39 mc. of radioactive chromic phosphate through five No. 22 gauge needles was accomplished.

The patient was admitted to the Veterans Hospital at Wood, Wisconsin on November 26, 1955 and died on November 29, 1955. On admission, he showed generalized icterus, multiple widespread petechiae and ecchymoses. There was a thrombocytopenia and afibrinogenemia noted, although exact figures are not available. Bone marrow studies showed metastatic carcinoma and generalized atrophy. Autopsy showed extensive metastatic carcinoma of the prostate and the cause of death was recorded as this plus the changes in the bone marrow and peripheral blood. Sections of the liver showed fatty degeneration and congestion with extramedullary hematopoiesis. The pathologist stated that the thrombocytopenia and icterus were hard to explain on the basis of findings. It is our impression that these changes may have been due to radiation damage.

Case 4. See figure 2. W. B. was admitted to the hospital on June 16, 1955 for control of diabetes and the nephrotic syndrome. On physical examination, a nodule was palpated in the prostate and a perineal biopsy of this nodule on July 8, 1955 was positive for adenocarcinoma of the prostate. On July 25, 1955

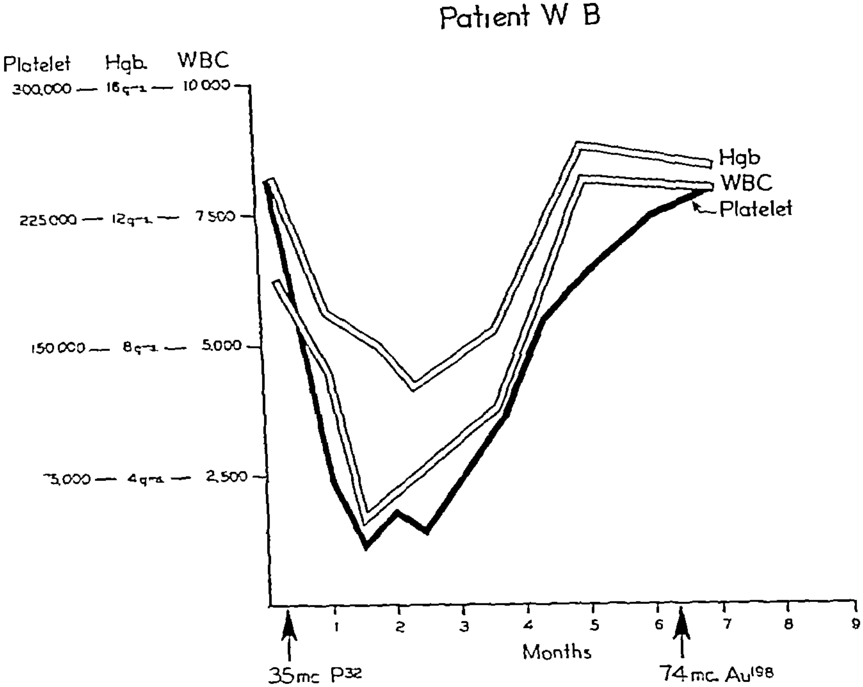

FIG 2

perineal injection of 35 mc of radioactive chromic phosphate was carried out using the technique described above

The patient went home and returned on August 6, 1955 for massive gastric hemorrhage An emergency gastric resection was done by the surgical service, however, the patient continued to bleed from the gastrointestinal tract for ten days following surgery Laboratory studies showed the platelet count to vary from a low of 28,000 to 164,000 and the white blood cell count to vary from a low of 2,000 to 4,800 He had multiple petechiae following surgery No bone marrow studies were done Recovery took place in several weeks

The patient was re-admitted on December 4, 1955 and laboratory studies revealed white blood cell count 8,700 with normal differential, hemoglobin 15 3 gm , hematocrit 44 per cent, platelets, 288,000, bleeding and coagulation times, normal, blood urea nitrogen, 12 4 mg per cent, and acid phosphatase 0 94 Bodansky units Needle biopsy of the liver showed fatty degeneration Needle biopsy of the kidney showed arteriolar nephrosclerosis Repeat biopsy of the prostate on December 14, 1955 showed adenocarcinoma of the prostate An injection of 74 mc of radioactive gold was done through five No 22 gauge needles introduced perineally

Followup examination on March 22, 1956 showed no softening of the gland on rectal examination No further complications ensued

It is probable that the severe gastric hemorrhage and changes in the blood

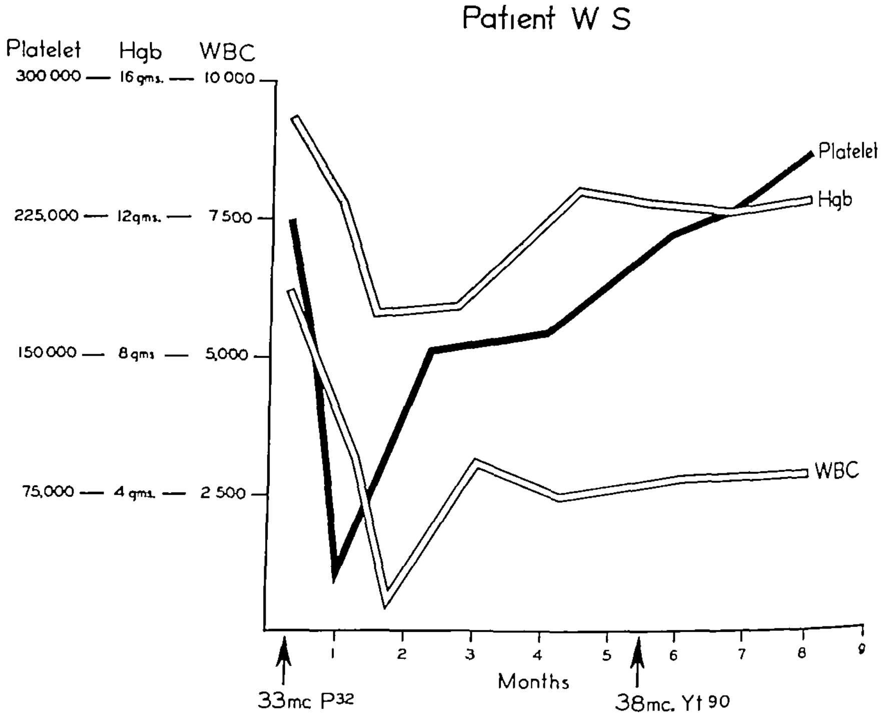

FIG 3

were due to bone marrow depression from radioactive chromic phosphate. At the time, we were not alert to such complications, or we would have avoided the gastric resection which was probably unnecessary.

Case 5. See figure 3. W. S. was admitted on July 22, 1955 complaining of low back pain and pain in the right hip. Rectally, the prostate felt typical of carcinoma with extension outside the capsule. X-rays showed no evidence of metastatic lesions. Laboratory studies: hemoglobin, 16.5 gm., hematocrit, 50 per cent, white blood cell count, 6,500, normal differential, blood urea nitrogen, 15.7 mg. per cent, acid phosphatase, 0.57 Bodansky units. Perineal biopsy showed adenocarcinoma of the prostate.

The prostatic mass was injected with 33 mc. of radioactive chromic phosphate using the usual technique. No immediate complications ensued.

The patient was re-admitted on September 7, 1955 for severe epistaxis, purpura and ecchymoses of the arms, legs, mouth and trunk. In addition, he had hematuria and was passing blood clots in the urine. The liver was palpable, smooth and not tender. The white blood cell count was 3,500 on admission and fell to 550 12 days later, and finally rose to 3,000 a month later. The platelet count was 24,000 on admission and rose to 54,000 ten days later and finally to 180,000. The hemoglobin was 14.6 gm. on admission and fell to 10.1 gm. and later rose to 14.1 gm. Bone marrow aspiration on September 12, 1955 showed markedly hypocellular marrow with depression of all elements. Repeat aspiration on October 28, 1955 showed an essentially normal marrow The patient made a good clinical recovery and it was believed that his pancytopenia was due to radiation effect on the bone marrow

The patient was re-admitted on January 4, 1956 and laboratory studies showed white blood cell count 2,900, normal differential, hemoglobin 15 3 gm , blood urea nitrogen, 15 mg per cent, platelets, 164,000, bleeding and coagulation times normal X-ray showed no metastases Repeat Silverman needle biopsy of the prostate showed active adenocarcinoma On January 17, 1956, 38 mc of radioactive yttrium was injected perineally

Followup visit on March 8, 1956 showed a platelet count of 220,000, hematocrit of 34 per cent and normal bleeding and coagulation times

Followup visit on April 12, 1956 revealed a hard, fixed, nodular prostate The patient was free of symptoms

Review of these cases seems to indicate that sufficient radiation damage to bone marrow with resultant pancytopenia occurred in four of the five patients receiving radioactive chromic phosphate In case 1, this was apparently directly related to the fatal outcome In case 3, the pancytopenia and fatal episode were probably due in part to radiation damage to the liver and bone marrow and in part to metastatic carcinomatosis Case 4 had a severe bleeding episode which was nearly fatal and from which he made an ultimate recovery, as did case 5 There seems to be little doubt that these latter 2 cases suffered from considerable radiation damage to hematopoietic organs Previous studies have shown that immediately following intraprostatic injection of radioactive chromic phosphate as much as 28 per cent of the total injected dose may be recovered from the circulating blood, and, certainly, some of this may become fixed in the bone marrow with resultant damage[1] The possibility also exists that some free phosphorus may be present in the colloidal suspension, and this, of course, would have a particular affinity for bone marrow

A recent report by Prout et al who reported hemorrhagic diathesis in metastatic prostatic carcinoma due to the production of a proteolytic enzyme produced by the carcinoma may account for some of the bleeding tendencies observed[2] Previous reports of Huggins and Vail,[3] Tagnon et al[4] and others all indicate that metastatic carcinoma of the prostate may produce a fibrinolysin leading to afibrinogenemia The role that these factors may play in the above cases is difficult to assess, but several of these patients did not have extensive metastatic disease, and, therefore, we feel that the blood changes were due chiefly to radiation change We have discontinued the use of radioactive chromic phosphate because of the above findings, and because we have failed to achieve any significant control of the carcinoma with this substance

Prout, G R Siegel M , Cliffton, E E and Whitmore, W F Hemorrhagic diathesis in patients with carcinoma of prostate J A M A , **160** 840–846, 1956

[3] Huggins, C and Vail V C Plasma coagulation and fibrinogenolysis by prostatic fluid and trypsin Am J Physiol **139** 129, 1943

[4] Tagnon, H J Whitmore, W F , Schulman, P and Kravitz S C The significance of fibrinolysis occurring in patients with metastatic cancer of the prostate Cancer **6** 63 1953

SUMMARY

Further experiences following the use of radioactive yttrium chloride seem to indicate that it has no advantage over radioactive gold in the treatment of patients with carcinoma of the prostate

Severe radiation damage to the bone marrow following the intraprostatic injection of radioactive chromic phosphate is reported and has led us to discontinue the use of this substance

Five patients failed to benefit clinically from the intraprostatic injection of radioactive chromic phosphate

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TREATMENT OF CANCER OF PROSTATE BY INTERSTITIAL INJECTION OF Au 198 STUDIES IN PROBLEM OF DISTRIBUTION

R H FLOCKS, H B ELKINS AND D CULP

From The Departments of Urology and Radiology, College of Medicine, State University of Iowa, Iowa City, Iowa

Since March 21, 1951, 389 patients with inoperable cancer of the prostate but without distant metastasis have had as their sole treatment, or as part of their treatment, the interstitial injection of the radioactive isotope of gold, Au 198 Our experiences with this therapy have been previously reported[1 2 3] We have emphasized the careful selection of patients—patients in good general condition with group 1 lesions which were definitely operable have been reserved for radical prostatectomy while those with evidences of distant spread, group 3, have been treated by conservative, palliative therapy Those with group 1 cancer who would not submit to radical operation or whose general condition made it unwise and those with locally inoperable lesions in good general condition and with no evidences of dissemination beyond the regional lymph nodes were chosen for this treatment It was emphasized also that the method showed promise, but that the problem most pressing for solution was that of adequate distribution of the radioactive material throughout the neoplasm

The objective of this therapy was not only to destroy the local lesion which could be eradicated by local excision as proven by the good results obtained in the stage 1 group by radical prostatectomy, but also to destroy neoplasm in the surrounding fascias, in the regional lymphatic channels and in regional lymph nodes It has been variously demonstrated that 1–1 5 mc of Au 198 per cc of tissue will achieve a cancerocidal response so that it would seem that if this could be achieved satisfactorily in the prostate, in the surrounding tissues and in the lymphatic channels and nodes without serious complications, our mission would be accomplished

It is the purpose of this report to discuss the problems of adequately distributing the radioactive material as outlined above upon the basis of clinical studies on the 389 patients thus far treated, and other experimental studies

DISTRIBUTION WITHIN THE PRIMARY CANCER ITSELF

In the vast majority of 389 cases the weight of the local lesion was under 80 gm so that a total dose of 80 mc well distributed within the prostatic tumor would be quite satisfactory if the material remained localized long enough It

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass , June 4–6, 1956

[1] Flocks, R H , Kerr, H D , Elkins, H B and Culp, D Treatment of carcinoma of the prostate by interstitial radiation with radioactive gold (Au 198) A preliminary report J Urol , 68 510, 1952

[2] Flocks, R H , Kerr, H D , Elkins, H B and Culp, D Treatment of carcinoma of the prostate by interstitial radiation with radioactive gold (Au 198) A followup report J Urol 71 628 1954

[3] Kerr, H D , Flocks, R H , Elkins, H B , Culp, D and Evans, T C Follow up study of one hundred cases of carcinoma of the prostate treated with radioactive gold Radiology, 64 637 1955

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R H FLOCKS, H B ELKINS AND D CULP

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Since March 21, 1951, 389 patients with inoperable cancer of the prostate but without distant metastasis have had as their sole treatment, or as part of their treatment, the interstitial injection of the radioactive isotope of gold, Au 198 Our experiences with this therapy have been previously reported[1 2 3] We have emphasized the careful selection of patients—patients in good general condition with group 1 lesions which were definitely operable have been reserved for radical prostatectomy while those with evidences of distant spread, group 3, have been treated by conservative, palliative therapy Those with group 1 cancer who would not submit to radical operation or whose general condition made it unwise and those with locally inoperable lesions in good general condition and with no evidences of dissemination beyond the regional lymph nodes were chosen for this treatment It was emphasized also that the method showed promise, but that the problem most pressing for solution was that of adequate distribution of the radioactive material throughout the neoplasm

The objective of this therapy was not only to destroy the local lesion which could be eradicated by local excision as proven by the good results obtained in the stage 1 group by radical prostatectomy, but also to destroy neoplasm in the surrounding fascias, in the regional lymphatic channels and in regional lymph nodes It has been variously demonstrated that 1–1 5 mc of Au 198 per cc of tissue will achieve a cancerocidal response so that it would seem that if this could be achieved satisfactorily in the prostate, in the surrounding tissues and in the lymphatic channels and nodes without serious complications, our mission would be accomplished

It is the purpose of this report to discuss the problems of adequately distributing the radioactive material as outlined above upon the basis of clinical studies on the 389 patients thus far treated, and other experimental studies

DISTRIBUTION WITHIN THE PRIMARY CANCER ITSELF

In the vast majority of 389 cases the weight of the local lesion was under 80 gm so that a total dose of 80 mc well distributed within the prostatic tumor would be quite satisfactory if the material remained localized long enough It

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass , June 4–6 1956

[1] Flocks R H Kerr, H D , Elkins H B and Culp D Treatment of carcinoma of the prostate by interstitial radiation with radioactive gold (Au 198) A preliminary report J Urol 68 510, 1952

Flocks R H Kerr H D Elkins H B and Culp D Treatment of carcinoma of the prostate by interstitial radiation with radioactive gold (Au 198) A followup report J Urol 71 628 1954

[3] Kerr H D Flocks R H Elkins H B , Culp, D and Evans T C Follow-up study of one hundred cases of carcinoma of the prostate treated with radioactive gold Radiology 64 637 1955

was found that satisfactory distribution of the major portion of the dose administered was very difficult to obtain at one sitting, but that attention to certain factors seemed to be of definite help These may be discussed under the headings of the addition of a spreading factor, the utilization of the fascial planes about the prostate, the volume of injection, the technique of injection, and multiple injections

Experiments in mice utilizing hyaluronidase as an additive to the solution to be injected have shown that this enhances distribution (fig 1) *In vitro* experiments in prostatic tissue seem to indicate that pretreatment of tissue with hyaluronidase would enhance distribution still further but this has not been done in patients The question has been raised as to whether the use of a spreading factor causes the material to leave the site of injection sooner than is desirable

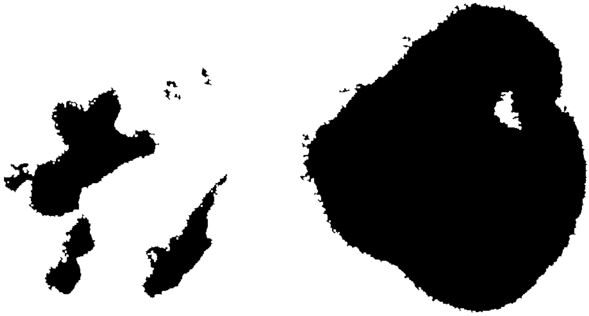


Fig 1 Radioautographs illustrating improvement in distribution of solution in mammary tumors of mice using hyaluronidase solution as diluent instead of saline Left shows autograph with saline Right shows autograph with use of hyaluronidase Note improvement

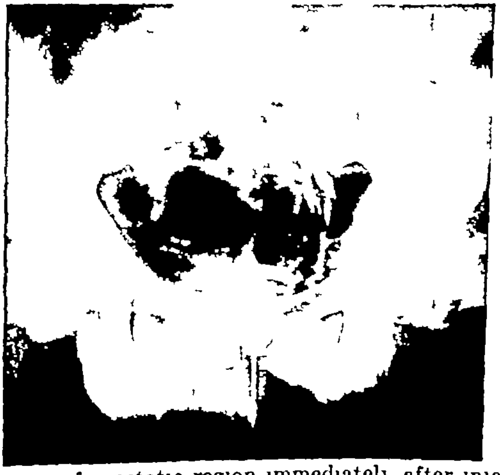


Fig 2 Roentgenogram of prostatic region immediately after injection of 4 cc 50 per cent diodrast solution into prostatic region Note that capacity of prostatic capsule has been exceeded and material has entered venous system

There is no clinical evidence to support this proposition On the contrary, there is clinical and experimental evidence to indicate that rapid entrance of the Au 198 into the bloodstream is associated with the use of an excessively large volume of diluent (fig 2)

The relatively small size of the average prostatic tumor and the anatomy of

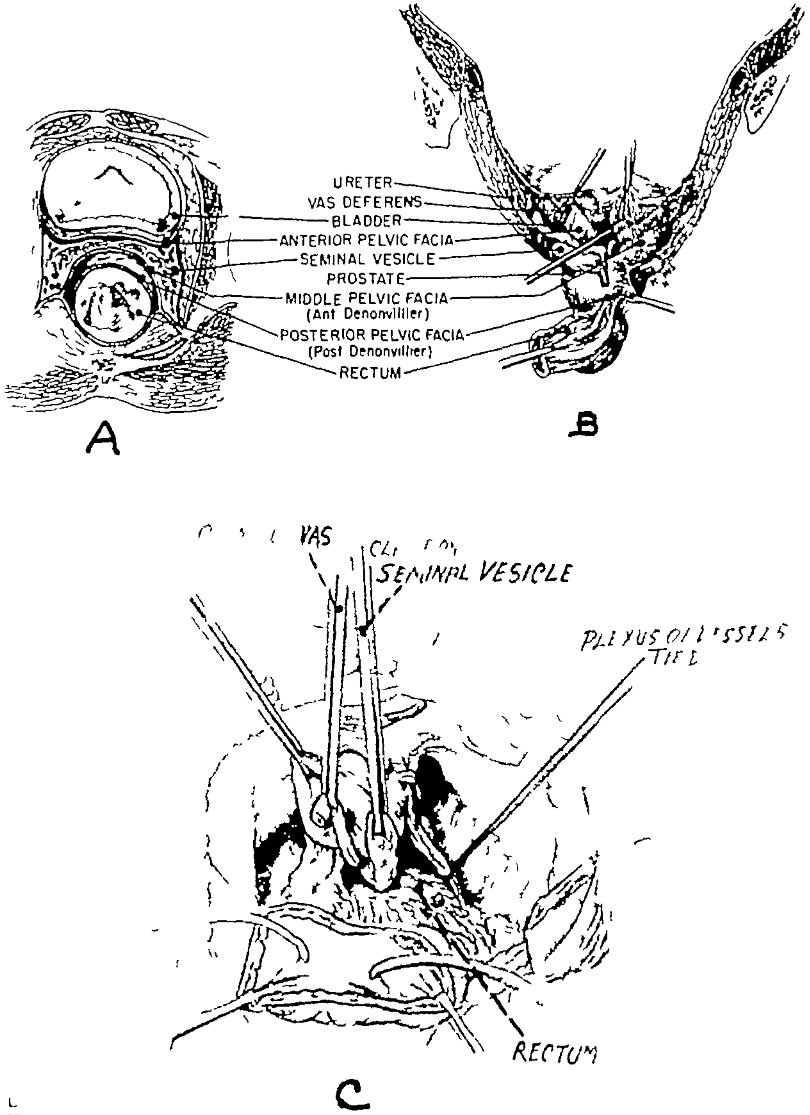


Fig 3 Studies of anatomy of fascial compartments about prostate and seminal vesicles Note relationship to rectum In C, drawing made during radical retropubic prostatectomy, note relationship of seminal vesicles and vascular pedicles to rectum Note that these are two separate fascial compartments

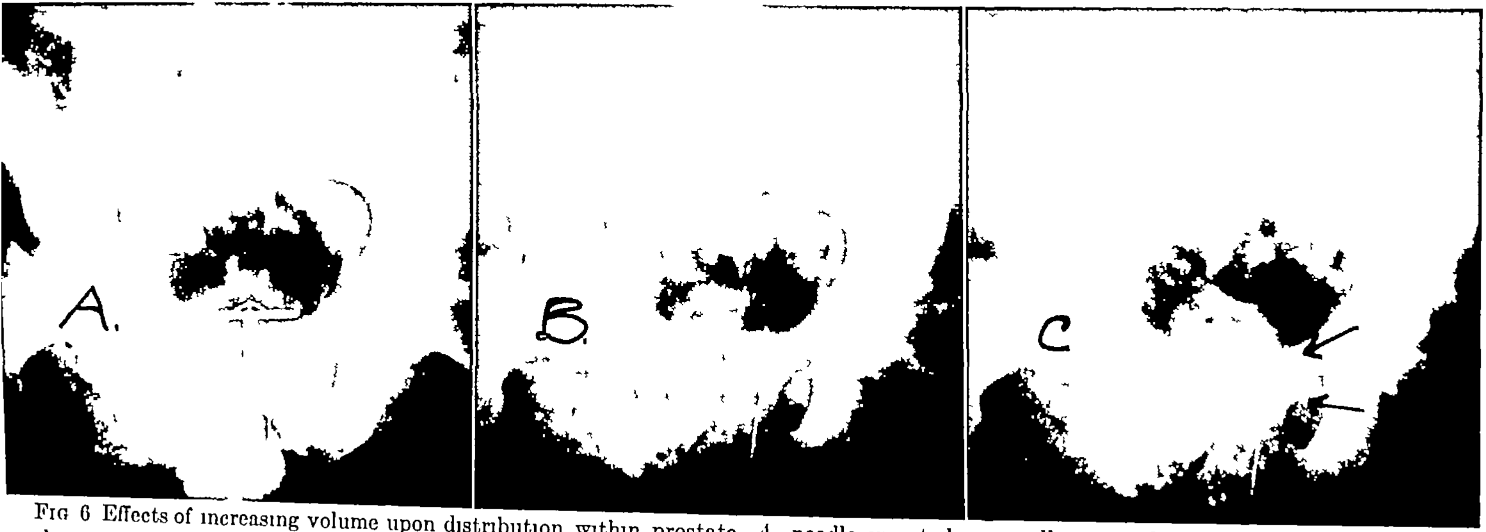


Fig 6 Effects of increasing volume upon distribution within prostate *A*, needle inserted perineally using long Lowsley tractor to help guide it into place *B*, 1 cc 70 per cent urokon solution injected Note that solution remained within prostate *C*, 2 cc solution injected Left side of prostate is filled to overflowing More volume would have led to extravasation outside prostate and probable venous entrance

lowing the intraprostatic septa with only 2 cc of material When the larger amount is used, notice breakthrough and spread into the fascial planes and into the veins This latter spread of the radiogold solution into the veins about the prostate and from these into the larger veins is very noticeable upon injection of large volumes of material and probably is the cause of the 7 to 15 per cent practically immediate appearance of the radioactive material in the bloodstream when more than 2 to 3 cc volume is used (fig 7) These are not related to the use of hyaluronidase and are not due to the rapid absorption of the material but are

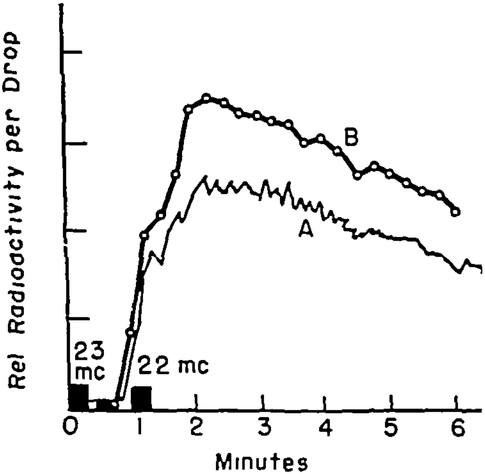


Fig 7 Chart showing almost immediate appearance of radioactivity in arterial blood of right arm following perineal injection of too large a volume of material (From work of Rounds in our laboratory)

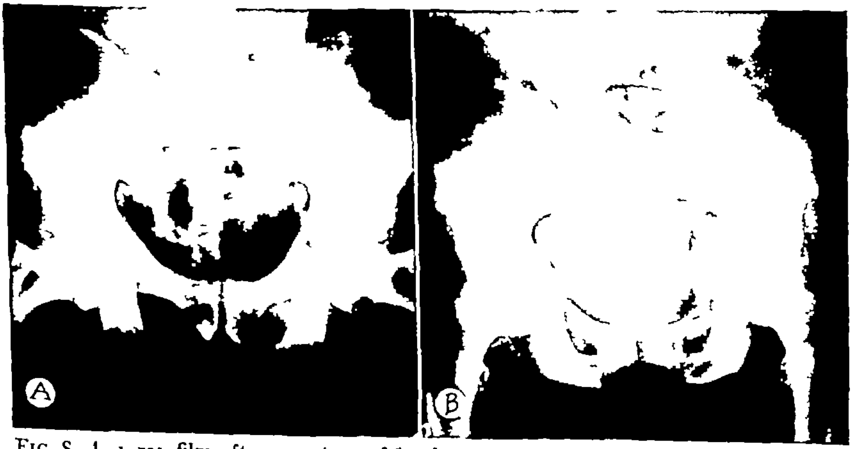


Fig 8 A, X ray film after injection of 1 solution containing 10 mc of Au 198 and ½ cc 70 per cent urokon Note good localization in residual carcinomatous nodule on right side *B* poor distribution of radioactive gold following perineal injection as demonstrated by 70 per cent urokon Secondary injection will be necessary No influence upon tumor nodule in left lateral lobe of prostate is to be expected In fact, since material was injected into and around bladder wall, bladder irritation may be expected here

rather due to the direct vascular entrance of the material by breaking into the veins in the prostate when large quantities of material are injected under moderate pressure It would seem from these studies that the use of pressure, when large quantities of material are used, is to be deprecated

If there is much scarring and a small volume is used there is little likelihood of marked spread of the injected solution (fig 8, *A*)

The technique of injection plays an important part in the obtaining of correct distribution Each fascial compartment should be entered and a small amount of the solution injected into it If the volume is too great the compartment will be broken open and leakage away from the desired area will occur If the wall of a compartment is punctured (fig 8, *B*) material will go to an undesired area and an undesirable result be obtained The best approach is the combined transvesical and extraprostatic (fig 9), but at times this is not possible and in such instances

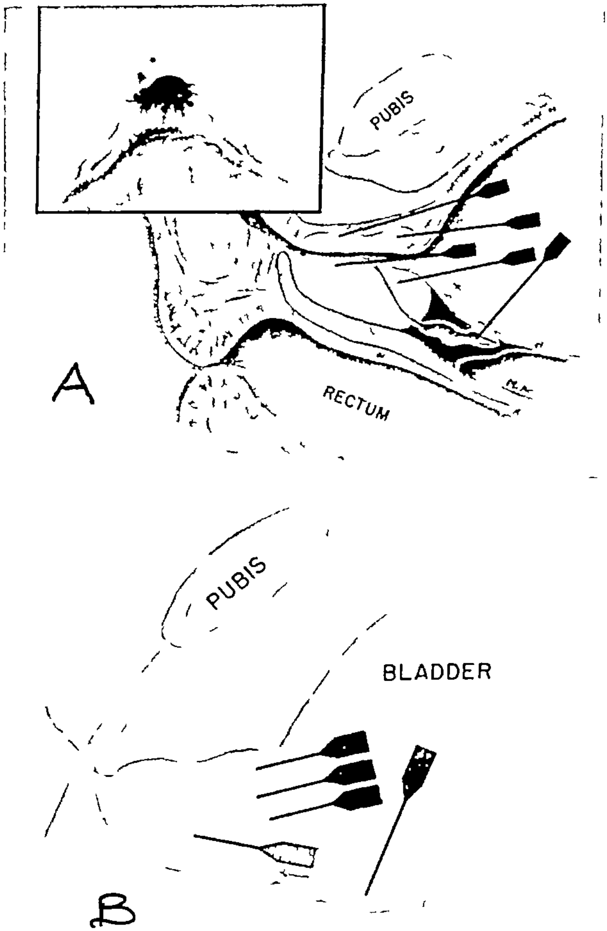


Fig 9 Diagrams illustrating combined transvesical, extraprostatic approach to injection of radioactive material

the closed perineal, open perineal, and transrectal routes may be used The fundamental principle is the laying down of multiple small volumes of the radioactive material throughout each compartment An example of such a good distribution is illustrated in figure 10

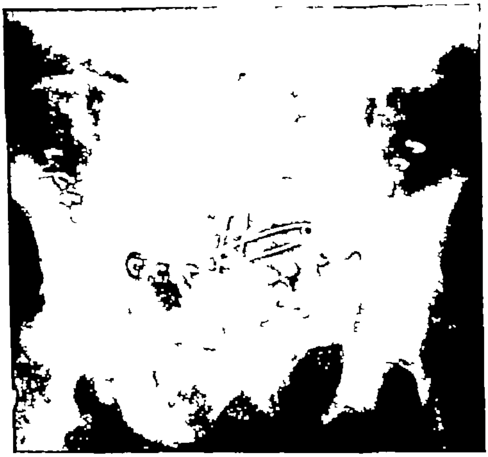
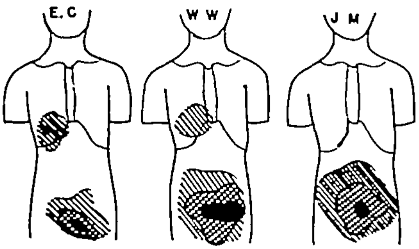


FIG 10 X ray film taken immediately after operation Note excellent distribution after combined transvesical and extraprostatic technique of injection

DISTRIBUTION OF RADIOGOLD IN 3 CASES

A After one day



B After five days

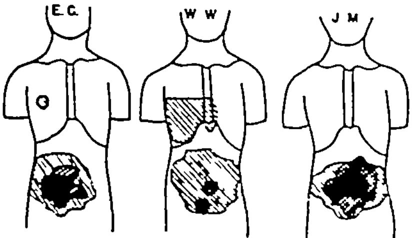


FIG 11 Post-injection radiation survey studies in 3 patients Note that 5 days after injection radioactivity is still localized in pelvic region

The question is sometimes asked, "How long does the material, after it is properly placed, stay in place? Does it stay in place long enough to produce the desired effect?" Post-injection radiation survey studies, in addition to clinical results, show that it does (fig 11)

In spite of the use of a correct volume, a correct dose, a correct distribution throughout the gland as far as the urokon x-ray film shows, some areas of carci

TABLE 2 *Route of administration*

	1 100	101-187	Total
Primary			
Retropubic-transvesical	89	60	149
Perineal	10	27	37
Transrectal	1	0	1
Secondary			
Retropubic-transvesical	1	2	3
Perineal	31	38	69
Transurethral resection	1	0	1
Number receiving			
1 Secondary injection	15	17	32
2 secondary injections	12	7	19
3 secondary injections	4	12	16
4 secondary injections	1	0	1
5 secondary injections	0	1	1

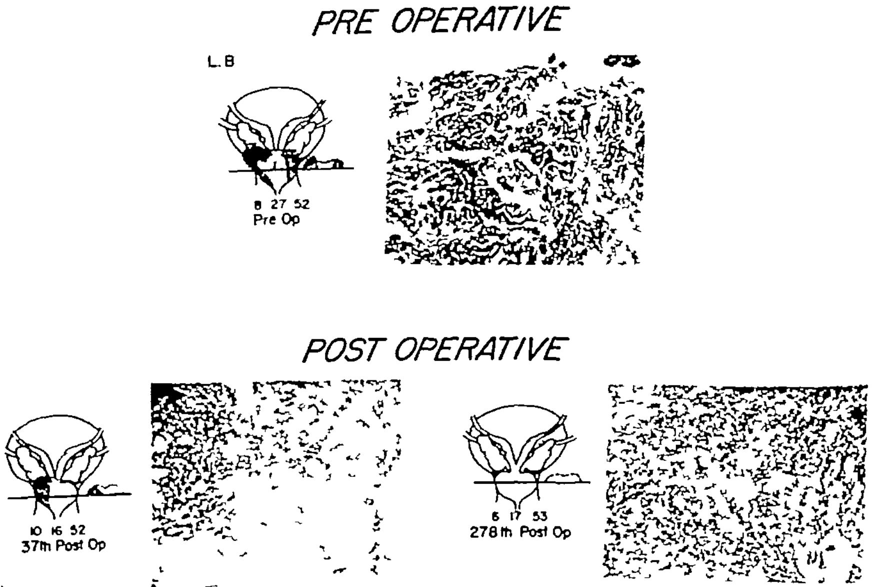


FIG 12 L B, 57-year old white man admitted 8 27 52 Note rectal findings after 2 months of estrogen therapy Received 125 mc injected by combined transvesical, extra prostatic route Note rectal findings 2 months later (10 16 52) Secondary injection at this time resulted in rectal findings as illustrated on 6 17 53 Two biopsies taken 1 year and 1 year, 6 months later by perineal punch and transurethral methods have been negative Prostate rectally has remained unchanged

noma may not be destroyed In this instance secondary injections are safe and are of great value Table 2 shows their incidence in our series, figure 12 illustrates their use in a patient followed by an excellent result

DISTRIBUTION TO ADJACENT FASCIAS AND ADJACENT LYMPH CHANNELS AND NODES

If the fascial compartments of the prostate and the seminal vesicles are not overfilled, little radiation, except from the gamma emission, will get to the areas about the prostate It is wise, therefore, to soak these areas with 10 to 15 mc or more on each side If gross masses of tumor are present, these should be infiltrated with the Au 198 just like the prostatic tissue was Even if the thin fascia does not hold the gold, it will get irradiated from the material which sticks to its surface and quite adequate irradiation obtained if the neoplasm present is not too thick If grossly involved nodes are present these must be removed surgically since adequate distribution throughout the node is difficult to obtain when large masses of tumor are present One of the striking facts observed in this group of 389 patients with local prostatic carcinoma was an incidence of 30 per cent grossly involved regional lymph nodes In many of these instances the local lesion was quite small The Au 198 distribution to uninvolved or very slightly involved regional lymph nodes from a well injected cancerous prostate, which was small enough to completely remove, is illustrated by the case in figures 13 and 14

Figure 13 illustrates the radioautograph of a prostate removed by retropubic radical prostatectomy following the injection 1 week previously of material in the apex of the prostate about an area of carcinoma which was considered operable It will be noted that the radioautograph shows sufficient counts to indicate a cancerocidal dose in a goodly area of the apex of the prostate and there is also, in the regional iliac nodes, a cancerocidal dose in some of these nodes None of these nodes were involved by carcinoma These studies indicate that properly injected material can produce a cancerocidal dose in a satisfactorily injected area and that a cancerocidal dose can be delivered to regional lymph nodes if the lymphatics to these are not blocked Figure 15 depicts microscopic sections through areas which show a positive radioautograph It will be noted that the material spreads fairly diffusely through the fascial connective tissue, giving multiple points of radioactivity It will be noted in figure 15, *B* that when carcinoma involves the areolar tissue and fatty tissue about the prostate, the spread of the material is not through the cords of cancer but through the areolar tissue carrying the nutritive vessels to and from the carcinoma

Recognizing the fact that the problem of distribution is an extremely important and difficult one, we have followed the course in many instances where large masses of carcinoma are present, obviously making the problem of distribution more difficult, of removing as much as possible of these masses Usually what is done is a radical prostatectomy, retropubically, with instillation of small amounts of the radioactive material into the surrounding pelvic fascia and into the prostatic pedicles At the same time, involved regional lymph nodes are removed We have followed this course in 10 instances and have found that aside from a somewhat more febrile convalescence the postoperative course was

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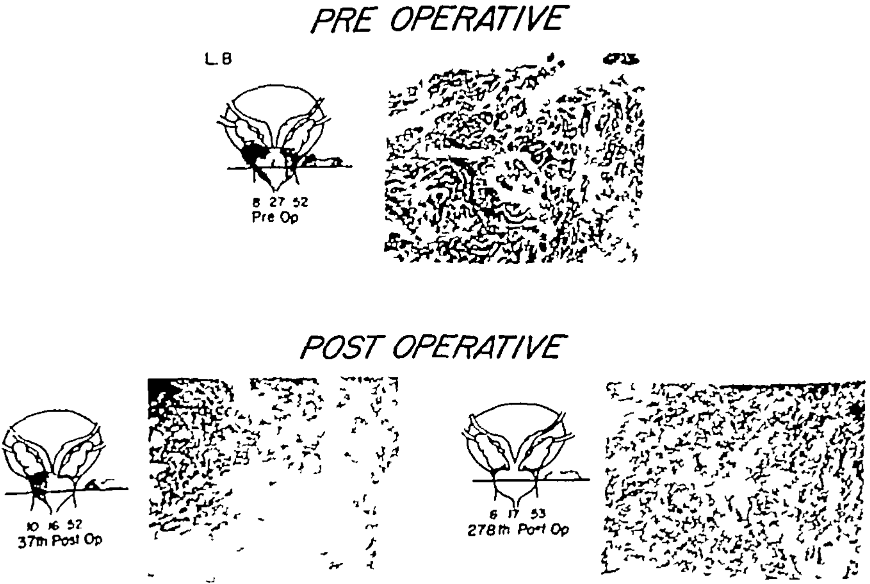

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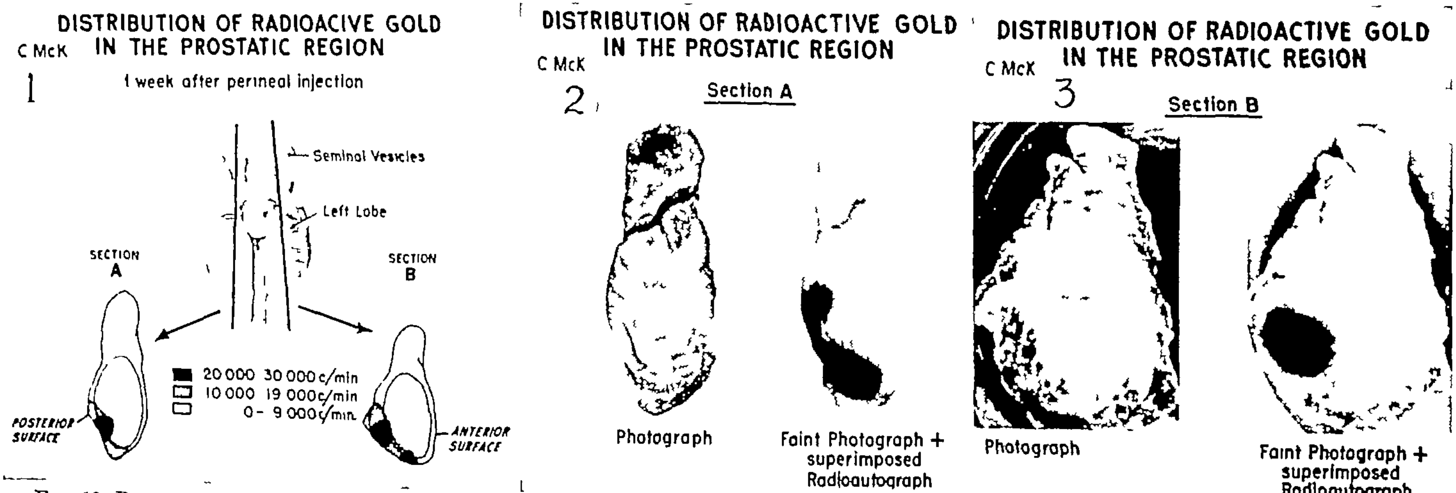

DISTRIBUTION OF RADIOACIVE GOLD IN THE PROSTATIC REGION
C McK
1
1 week after perineal injection
Seminal Vesicles
Left Lobe
SECTION A
SECTION B
POSTERIOR SURFACE
ANTERIOR SURFACE
■ 20 000 30 000 c/min
□ 10 000 19 000 c/min
□ 0 - 9 000 c/min
DISTRIBUTION OF RADIOACTIVE GOLD IN THE PROSTATIC REGION
C McK
2
Section A
Photograph
Faint Photograph + superimposed Radioautograph
DISTRIBUTION OF RADIOACTIVE GOLD IN THE PROSTATIC REGION
C McK
3
Section B
Photograph
Faint Photograph + superimposed Radioautograph

FIG 13 Distribution of radioactive gold in prostatic region 1 week after the injection of mc of radioactive gold into a hard area in the apex of the prostate which was an operable prostatic cancer *1*, Diagram showing removed prostate and adnexa and location of radioactivity *2*, Gross radioautograph of right lateral lobe *3*, Gross radioautograph of left lateral lobe

IN THE PROSTATE

A

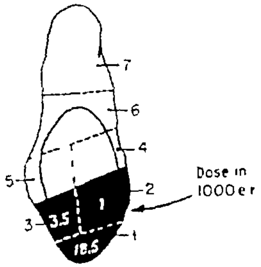
C McK

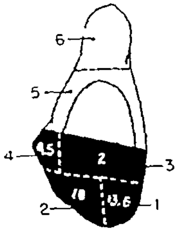
Right Lobe

PORTION	WEIGHT gms	μc	CORR for DECAY	er
1	0 9	36 5	219 0	16 500
2	1 45	2 6	16 5	660
3	1 95	14 9	89 4	3,500
4	2 3	0	0	
5	3 8	0 5	16 8	340
6	5	0	0	
7	3 5	0	0	

Left Lobe

PORTION	WEIGHT gms.	μc	CORR. for DECAY	er
1	1 5	45 5	270	13 600
2	1 15	24 5	147	10 000
3	5 7	24 5	147	1,970
4	–	57 0	342	4 550
5	6 0	2 5	15	195
6	3 5	0	0	
Lymph Node (all)	0 5	15 4	92 4	14 000



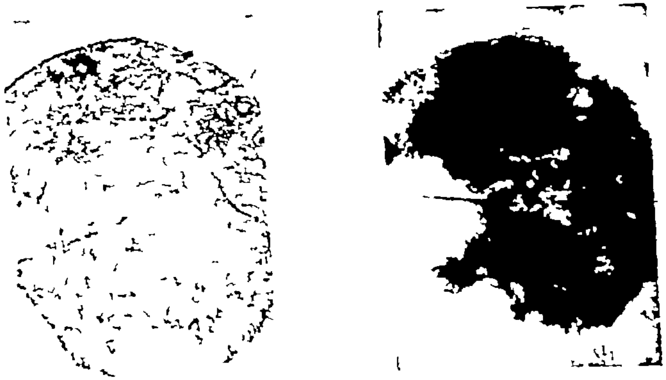


DISTRIBUTION OF RADIOACTIVE GOLD IN THE PROSTATIC REGION

B.

C McK

Right External Iliac Node



Photograph

Photograph + Radioautograph

FIG 14 Distribution of radioactive gold in prostatic region 1 week after injection of 30 mc of radioactive gold into a hard area in the apex of the prostate which was considered an operable prostatic cancer Same case as figure 13 A note that lobes have been divided off into sections and estimated roentgens of energy delivered to these sections are shown in charts Note that "probable" cancerocidal dose has been delivered to section 1 of right lateral lobe and sections 1, 2 and 4 of left lateral lobe Note, in lower line of chart under left lobe, that dose to right iliac node removed was "probably" also cancerocidal *B* photograph and radioautograph of the lymph node removed Note marked concentration of radioactivity in outer portion of node No nodes in this patient were grossly involved with cancer This node was removed simply for study with regard to its radioactivity

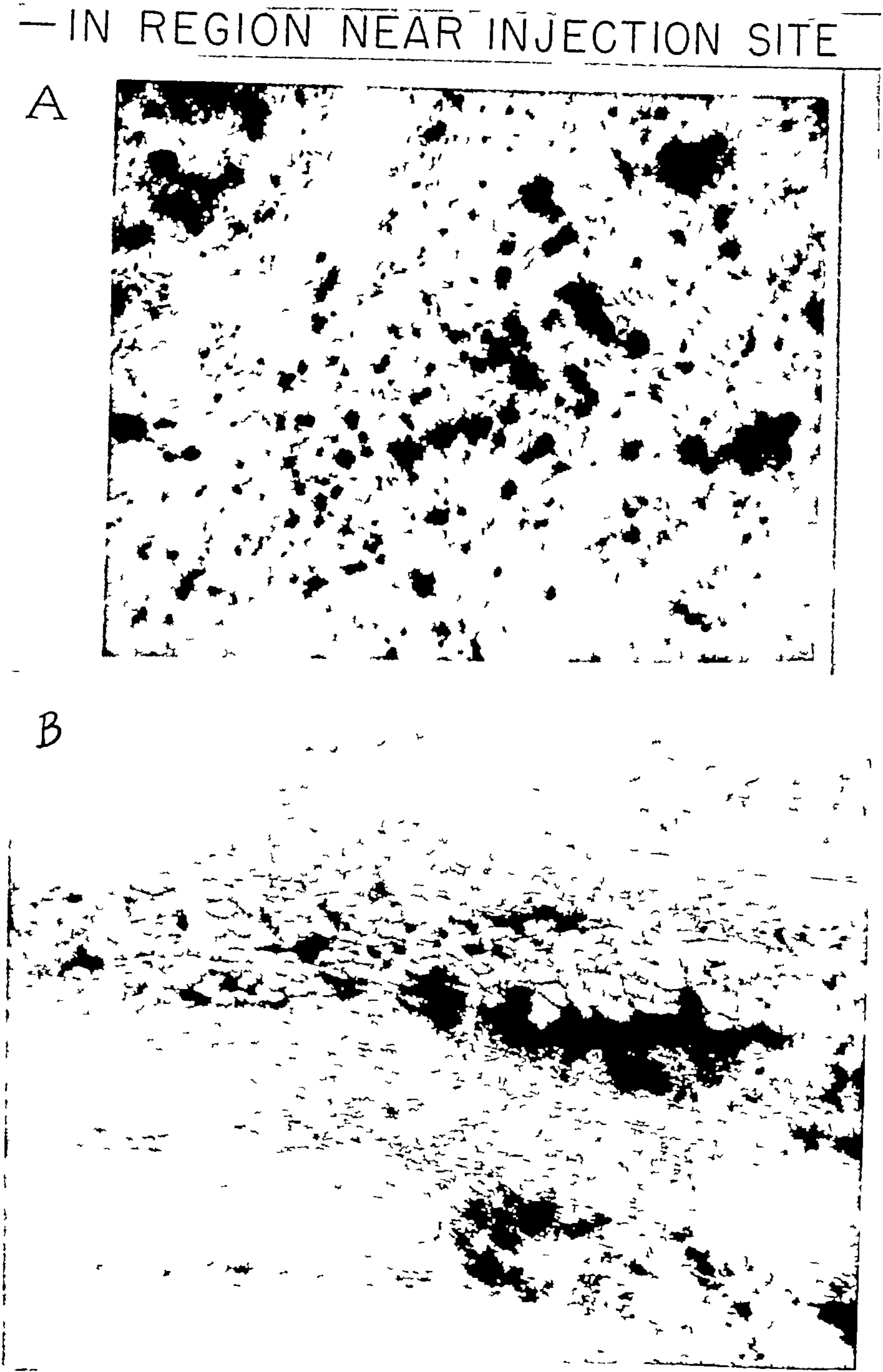


Fig 15 *A*, microscopic section and superimposed radioautograph of well injected area of prostatic cancer 1 week after injection

B, radioautograph superimposed upon microscopic section of tissue outside prostatic capsule markedly invaded by neoplasm Note that radioactive material travels in areolar tissue around growing cords of neoplastic tissue

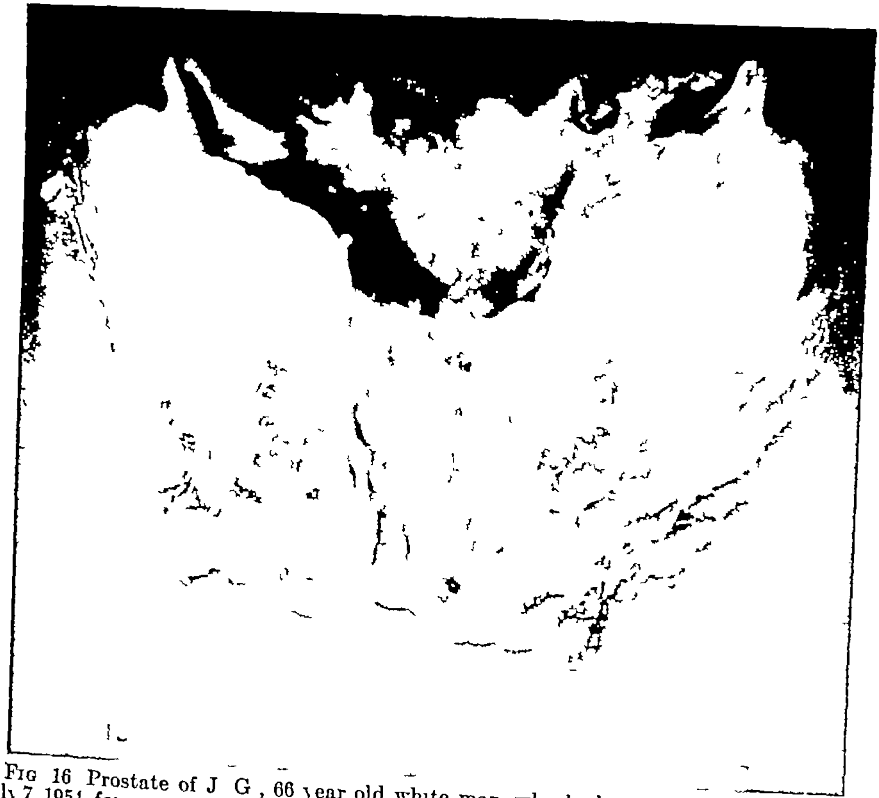
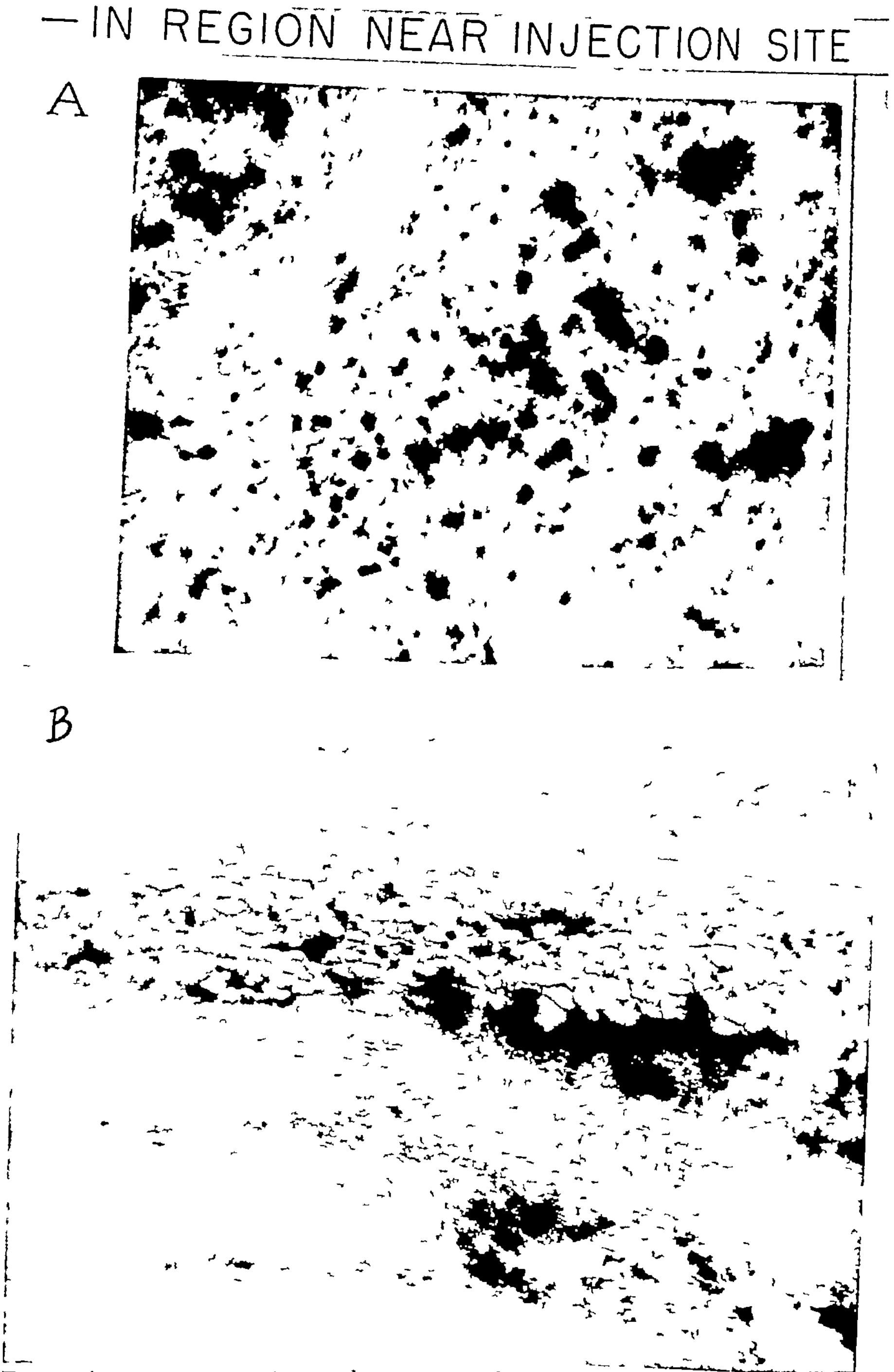


FIG 16 Prostate of J G , 66 year old white man, who had transurethral resection on July 7, 1954, for carcinoma of prostate with retention On July 22, 1954, retropubic exposure of prostate was carried out No enlarged regional lymph nodes were found Prostate was seat of large cancer involving both lateral lobes, anterior lobe, subtrigonal area and both semi nal vesicles There was induration lateral from prostate on each side By sharp dissection, prostate and as much of seminal vesicles, subtrigonal area, and prostatic pedicles were removed Pedicles and adjacent areas on each side were infiltrated with a total of 50 mc radioactive gold in 3 cc diluent Postoperative course was uneventful Patient as of March 1956 was well with nothing palpable rectally which might indicate neoplasm, and voiding well No endocrine therapy of any kind was being used Of course, it is still too early to know about ultimate result but result 20 months after therapy is satisfactory

essentially unchanged, there was no evidence of damage to the rectum in any case and the results were quite good In some instances apparent cures were obtained In others, although healing of the wound, etc took place, carcinoma recurred with the requirement of further palliative therapy A good example of such therapy is indicated in figure 16

In conclusion, studies of the problems connected with the distribution of the radioactive material through the cancerous prostate have shown that satisfactory distribution can be obtained in many instances Some of the factors which seem to be of help in obtaining such distribution are 1) the use of hyaluronidase as a spreading factor, 2) the use of very small volumes of material to carry the required radioactive dose, 3) proper utilization of fascial septa and fascial planes,



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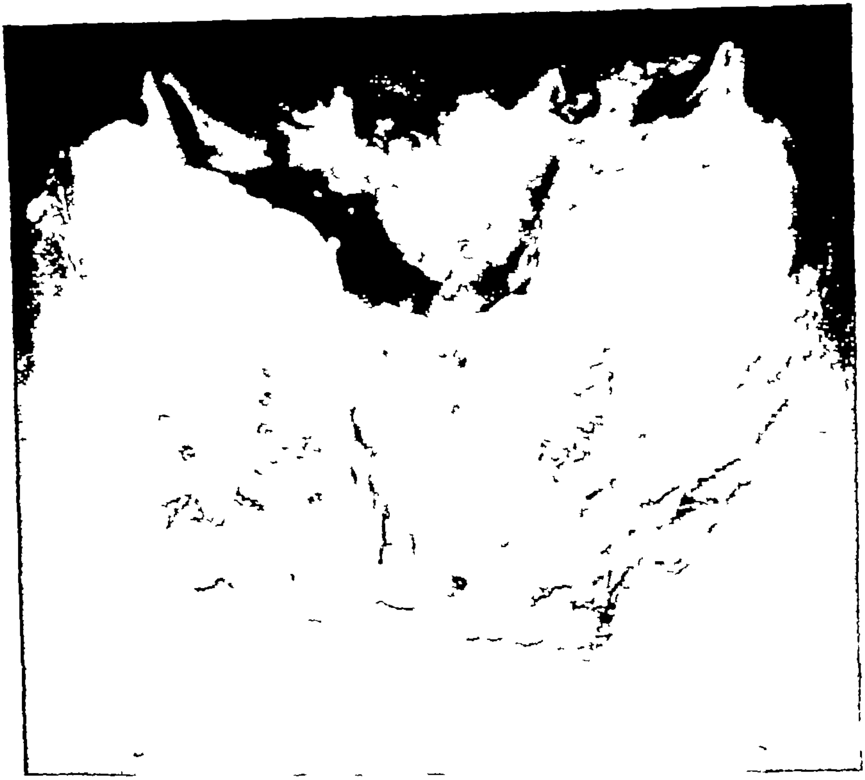

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4) the utilization of technique for studying distribution after injection, such as the use of urokon or diodrast as a diluent, and postoperative radiation surveys, 5) multiple injections at 2 month intervals, and 6) the removal of masses of tissue and grossly involved lymph nodes to reduce the amount of tissue which needs to be irradiated, thus cutting down on the danger of obtaining inadequate distribution and on the need of using very large total and therefore relatively dangerous doses of radioactive material

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AN EVALUATION OF ENDOCRINE CONTROL THERAPY PLUS RADICAL PERINEAL PROSTATECTOMY IN THE TREATMENT OF SELECTED CASES OF ADVANCED CARCINOMA OF THE PROSTATE FOLLOWED FIVE OR MORE YEARS

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The marked regression of primary carcinomatous lesions of the prostate that often results from endocrine control therapy has suggested to a number of observers a broadened field of usefulness for the radical perineal prostatectomy. Vallett, in 1944, seems to have been the first to use this combined therapy but, unfortunately, the patient died too soon after surgery to permit any conclusions as to its efficacy. Later in that year Parlow and then Colston suggested its use in selected cases. In December of the same year, Scott and Benjamin reported 2 cases of advanced carcinoma of the prostate without metastases, that had been treated by this method. One of these patients is alive and apparently free from tumor at this time. Colston and Brendler, in 1947, reported 1 death in 7 cases that had been followed 2 years after surgery. In 1949 Parlow and Scott presented their early results in 14 cases. The same year Gutierrez, in reporting 9 cases, expressed the opinion that the operability of advanced cases of carcinoma of the prostate would be markedly increased by this method. One year later Scott and Parlow presented a detailed report on the first 13 of 22 patients who had been treated by the combined therapy and were apparently free from tumor. Scott, in 1952, in presenting a detailed report on 21 consecutive patients treated in this manner and followed 3 or more years after therapy had been started, reported a survival rate of 85.7 per cent. The following year Sullivan and Hartwig reported that they had used this therapy in the treatment of 10 patients with advanced carcinoma of the prostate. Although the number of patients treated by this method in our clinic and followed 5 or more years is small, consisting of but 29 consecutive cases, we believe our results are sufficiently encouraging to warrant their presentation at this time.

Since an evaluation of the effectiveness of this combined therapy in the treatment of selected cases of advanced carcinoma of the prostate gland is necessarily influenced by the type of case included in such a study, it might be helpful if our criteria for the selection of cases were presented at this time. Obviously, those patients in whom the carcinoma, because of recent origin or latency of growth when first discovered, is so situated as to permit a reasonable chance for its complete removal by radical surgery, should not be included in this group. No patients with proven metastases, when first seen, are considered suitable candidates for the follow-up radical perineal prostatectomy, regardless of their apparently favorable response to endocrine control therapy. If the local growth has advanced enough to result in the formation of a well-defined intervesicular

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plateau or has extended for a considerable distance over one seminal vesicle when the patient is first seen, it seems reasonable to assume that invasion beyond the palpable area may have occurred even though the presence of metastases cannot be proven In such cases, regardless of a remarkable local response, our experiences suggest that, although the follow-up radical prostatectomy may increase the patient's life expectancy and freedom from distressing urinary symptoms, it still must be considered of questionable value However, when the cases belonging in the above categories have been excluded, there still remains a number of patients with advanced carcinoma of the prostate for whom the combined therapy may be most helpful

These are the patients without metastasis in whom the carcinomatous extension beyond the confines of the prostate, while not marked, is too great to permit its complete extirpation by radical surgery when the patient is first examined It is for these patients, provided their response to endocrine therapy has been such that a digital examination at the time of maximum regression suggests that complete extirpation of the carcinomatous lesion might be possible, that we believe a follow-up radical perineal prostatectomy offers a chance for a cure or, failing in this, will at least prolong the patient's life and freedom from distressing symptoms But even some of these patients have to be excluded because advanced age or their general physical condition seems to contraindicate radical surgery

It seems to us that the decision as to whether or not the patient is a suitable candidate for radical surgery is less difficult to make on the basis of his age than from the standpoint of his general physical condition Because of their limited life expectancy and because carcinoma of the prostate often progresses very slowly in patients who are 75 or more years of age, we have not used the combined therapy in any instance in which the patient was that old when first seen We have learned that, as a result of careful preoperative and postoperative care, proper supporting measures during operation, and the availability of very satisfactory antibiotics, the radical perineal prostatectomy, while requiring a little longer to perform, is seldom more disturbing to the patient than some of the more commonly used surgical procedures upon the prostate At least 5 of our patients had a history of coronary disease with cardiographic evidence of damage and yet were no more disturbed by the operation than the average case As a rule, the operative risk caused by the presence of general physical debility is little, if any, greater than that of the other open operations upon the prostate for the correction of prostatic obstruction

SUMMARY OF RESULTS AND DISCUSSION

The results of endocrine therapy plus the radical perineal prostatectomy in 29 consecutive, selected cases of advanced carcinoma of the prostate without metastases when first seen, and followed 5 or more years after treatment was started, have been most encouraging Although in 23 of the cases the clinical impression of carcinoma was confirmed by biopsy studies made either before or very shortly after endocrine therapy had been instituted, the decision to operate was in no was influenced by the pathological characteristics of the tissue examined. The blood studies and renal function tests were within normal limits at the time of operation. Our first patient is well and apparently free from tumor 168 months after endocrine therapy was started and 128 months after radical surgery. Among our surviving patients in this series, the shortest time that has elapsed since the institution of therapy is 70 months, and after surgery 67 months. Nine patients or 31.1 per cent died within 60 months from the time therapy was started. However, in 4 instances or 44.4 per cent of these there was no evidence of local recurrence or metastatic prostatic carcinoma at the time of death.

The cases in which death due to cancer occurred within 5 years have been reviewed in a search for the causative factors of failure. One patient, in whom carcinomatous tissue was left at operation in the region of one seminal vesicle, died of cancer 14 months after treatment was started and 7 months after surgery. This patient had definite extension over both seminal vesicles with intervesicular plateau formation before treatment was started. Another patient with carcinomatous extension from the left lobe, causing a small nodular involvement of the vesical neck when first seen, died of metastases 28 months after treatment was started and 18 months after radical prostatectomy. There was no evidence of local recurrence. A third patient with involvement of the left lobe and extension into the membranous urethra on first examination died 36 months after estrogen therapy was started and 33 months after radical prostatectomy. Perineural lymphatic involvement probably beyond the surgical field was found on the pathological examination of the tissue removed. Bilateral orchiectomy 15 months and bilateral adrenalectomy 17 months after the prostatectomy were not effective. In another patient an involvement of the left lateral lobe with extension to the membranous urethra seemed to have completely disappeared under 11 months of endocrine control therapy. However, in spite of the fact that no typical active areas of carcinoma were found on microscopic study of many sections from the surgical specimen, the patient died of a local recurrence with metastasis 34 months after surgery. The fifth patient died of cancer 58 months after treatment was started and 40 months after surgery. He had extensive involvement over the seminal vesicles when first seen and pathological studies of the surgical specimen showed evidence of extension beyond the operative field.

In the group of patients who survived more than 5 years after operation, one died of cancer and two others are living with recurrence. The death occurred 78 months after treatment was started and 72 months after radical surgery in a patient with considerable extension over the seminal vesicles and intervesicular plateau formation, when first seen. Pathological studies of the surgical specimen indicated extension beyond the operative field. Furthermore, the patient was not placed on postoperative estrogen therapy until 42 months after surgery when the recurrence was discovered. In one patient with extension into the membranous urethra from the left lobe of the prostate, recurrence was discovered 45 months after estrogen therapy was started and 35 months after prostatectomy. He refused control therapy after his operation until the recurrence was discovered. At this time a bilateral orchiectomy was performed and he was placed back on estrogen plateau or has extended for a considerable distance over one seminal vesicle when the patient is first seen, it seems reasonable to assume that invasion beyond the palpable area may have occurred even though the presence of metastases cannot be proven In such cases, regardless of a remarkable local response, our experiences suggest that, although the follow-up radical prostatectomy may increase the patient's life expectancy and freedom from distressing urinary symptoms, it still must be considered of questionable value However, when the cases belonging in the above categories have been excluded, there still remains a number of patients with advanced carcinoma of the prostate for whom the combined therapy may be most helpful

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A study of our 6 patients who died of cancer and the two living with recurrence, for the purpose of explaining our failures, suggests at least two contributing factors The first is related to the extent and location of the carcinomatous lesion when the patient is first seen Deaths occurred in 3 instances where the growth had extended over the seminal vesicles, resulting in the presence of an inter vesicular plateau In 2 other cases there was extension from the lateral lobe into the membranous urethra and in another there was secondary involvement of the bladder in the region of the vesical neck In a patient who died of cancer more than 5 years after the start of therapy and in two others who are living with recurrence, inadequate postoperative endocrine therapy may well have been a contributing factor It is our firm belief that in treating cancer, especially the cases in this particular group, we should utilize as soon as possible and to the fullest extent, all the effective measures we have at our command Where the patient will consent he should be prepared for surgery by estrogen therapy plus bilateral orchiectomy and after operation he should be maintained on estrogen therapy for several years

Fortunately, there are now available sufficient reliable data to permit a very satisfactory evaluation of the relative effectiveness of the various types of therapy used in treatment of patients with advanced as well as supposedly confined carcinoma of the prostate, who were without metastases when first seen As a control series we have the report by Nesbit and Plumb on the survival rate at 6 month intervals on 273 cases that were treated by the methods in use before the introduction of endocrine therapy and followed for 60 months after their first visit Using the case material supplied by the members of the Urosurgical Society, Nesbit and Baum, in 1950, reported the survival rate at 6 month intervals for 60 months on a series of 324 cases of advanced carcinoma of the prostate without metastasis, that were treated by the various types of endocrine therapy that are in common use today To the above we have added our series of 29 consecutive, selected cases of advanced carcinoma of the prostate without metastasis when first seen, that were treated by endocrine therapy plus the radical perineal prostatectomy, and also a series reported by Jewett of 78 cases of carcinoma of the prostate without metastasis, in which there was no evidence of extraprostatic extension prior to the time of the radical perineal prostatectomy In the latter series endocrine therapy was not used

One cannot examine the results of the various types of therapy presented in table 1 without being deeply impressed by the progress that has been made in the treatment of cancer of the prostate gland during the past two decades Whereas the survival rate for 60 months was but 10 per cent in the control group it was 29 per cent in the diethylstilbestrol series, 31 2 per cent in the castration cases, 43 6 per cent where estrogen and castration were combined and 68 9 per cent in the group treated by endocrine therapy plus the radical perineal prostatectomy It would seem that, inasmuch as extension beyond the confines of the prostate was present to some degree in all our cases when first seen and whereas there was no apparent extraprostatic involvement in the group reported by Jewett, the 68 9 per cent 5-year survival rate in the former compares very favorably with the 51 3 per cent in the latter The higher 5-year survival rate in our series might be explained in part, at least, by the fact that in every case a favorable response to endocrine therapy had been demonstrated Although it is perhaps unwise to attach too much significance to the results of a comparative study in which one group is considerably smaller than the others, it is interesting to note that the percentage of deaths not attributable to cancer, in this group, was greater than that of any of the others

In the treatment of selected cases of advanced carcinoma of the prostate without metastases when first seen, endocrine therapy and the radical follow-up perineal prostatectomy seem to complement each other very nicely Sometimes in the cases where the extraprostatic extension is too marked to permit complete

TABLE 1 *Type of therapy and percentage survival at 6 month intervals in series of cases of carcinoma of the prostate without metastases at time of first visit*

Type of therapy	Number of cases	% Survival at six month intervals										% deaths not from prostatic cancer
		6	12	18	24	30	36	42	48	54	60	
Control (Nesbit and Plumb)	273	72 0	54 0	39 0	32 0	25 0	22 0	—	14	—	*10*	—
Diethylstilbestrol (Nesbit and Baum)	63	93 7	88 9	82 6	76 2	63 5	55 6	43 0	33 5	31 0	29	32
Castration (Nesbit and Baum)	183	90 8	83 7	72 0	65 1	61 3	51 4	45 0	37 7	35 0	31 2	22
Diethylstilbestrol and castration (Nesbit and Baum)	78	93 6	84 7	80 8	74 4	71 8	65 4	57 8	53 9	53 9	43 6	30
Endocrine therapy plus radical perineal prostatectomy (Scott)	29	100 0	100 0	96 5	96 5	93 1	89 6	79 3	79 3	72 4	68 9	44 4
Radical perineal prostatectomy no endocrine therapy (Jewett)	78	(without preoperative evidence of extraprostatic extension) (recurrence in 24 cases)									51 3	36 4
Total	704											

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Endocrine therapy plus radical perineal prostatectomy (Scott)	29	100.0	100.0	96.5	96.5	93.1	89.6	79.3	79.3	72.4	68.9	44.4
Radical perineal prostatectomy no endocrine therapy Jewett)	78	(without preoperative evidence of extraprostatic extension) (recurrence in 24 cases)									51.3	36.4
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extirpation when the patient is first seen, the initial response to endocrine therapy is such as to make this procedure possible at a future date Furthermore, it would seem that the damaging effect of endocrine therapy upon the cancer cells within the prostatic capsule might tend to decrease the possibility of local and distant spread at the time of surgery Postoperative endocrine therapy is necessary to destroy, or failing in this, to stem the growth and spread of any small foci of cancer that may have been left at surgery We believe that, even where there is no evidence of extraprostatic extension when the patient is first seen, he should be maintained on a postoperative course of estrogen therapy for at least 4 years after the radical perineal prostatectomy Finally, the follow-up radical perineal prostatectomy removes the source from which local extension may recur and metastases spread, once the effectiveness of the hormone control therapy has been lost

We think that our results are sufficiently encouraging to warrant further trial of this therapy Even if in our remaining cases the carcinoma is not so satisfactorily controlled, we believe that this treatment in most instances, when judiciously used, will prolong the life of the patient and increase his period of freedom from the distressing urinary symptoms that almost inevitably accompany the late stages of this disease As pointed out previously, the operation entails little or no more risk than other open operations for relief of prostatic obstruction Furthermore, Vest's introduction of the traction-suture method of anastomosing the vesical neck and the membranous urethra has done much to prevent the incontinence that has occasionally resulted from this type of surgery

CONCLUSIONS

The results obtained by endocrine therapy plus a follow-up radical perineal prostatectomy in the treatment of 29 consecutive *selected* cases of advanced carcinoma of the prostate without metastasis when first seen have been presented

The survival rate of 68 9 per cent for 5 years is apparently better than has been obtained in the treatment of similar cases by any of the other methods in common use today

Although this report has not been submitted as an evaluation of the ultimate mortality in such cases, we believe the results warrant a further trial of this therapy

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not in effect alter a person's sex as indicated by the gonadal pattern It was known that the psychic pattern might vary from the gonadal type and that it could be very much influenced by training Also, it was appreciated that every individual formed and excreted some hormones of the opposite sex, and that every one was to some degree a mixture of characteristics from both sexes However, it was felt that the gonad was the definite arbiter and final determinant of sex

The change in the idea of what constitutes a person's sex has been evolving for many years and some findings of the last few years have made most necessary a revision of our thoughts on the subject It is not easy to define just what sex is as it applies to an individual It is almost a philosophical as well as a medical question and I think we can best approach it by reviewing first what attributes or features determine sex

The first and most basic feature which determines sex is the chromosome pattern of the individual's cells Briefly, we recall that the sex chromosome in females is made up of two X elements, while the male sex chromosome is made up of an X and a Y element When the sex chromosome divides during maturation, each ovum, therefore, carries an X element while half the sperm carry an X and half carry a Y Depending on which kind of sperm unites with the ovum at fertilization, the resulting individual carries an XX or XY sex chromosome in each of its cells Up until the last year or so, it was thought that the individual's clinical sex always corresponded to the chromosomal sex Recent evidence indicates that this is not so For instance, patients with gonadal dysgenesis, formerly called ovarian agenesis or Turner's syndrome, who were considered to be female, have now been found in most cases to have the XY chromosome complex On the other hand, patients with testicular hypoplasia and the so-called Klinefelter syndrome (or more properly Bronstein-Klinefelter syndrome, since it was first described by Dr Bronstein), have male characteristics, but have been found in some cases to have a female XX chromosome complex

The next most important factor that determines sex is the nature of the gonads For many years, as mentioned before, this was considered the best indicator of the true sex of the individual The primitive gonad is indeterminate, and during development there are periods in which the gonadal pattern of first one sex and then the other is predominant The conversion of a gonad of one type to that of another type is not entirely out of the realm of possibility (and has been accomplished experimentally in insects)

The next factor in the determination of sex is the hormonal pattern The hormonal effect on the growth and development of various tissues and organs is one of the mechanisms by which the gonads regulate and influence sexual development However, we find that hormones from extragonadal sources also can drastically alter the development of sex features

The most obvious group of factors determining clinical sex are the sex organs, including the internal and external genitalia and the secondary sex characteristics Most important of these are the external and internal genitalia, namely, the duct and glandular structures and copulatory organs The secondary sex characteristics include the general overall body structure, breast development,

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RECENT ADVANCES IN THE MANAGEMENT OF THE INTERSEX PATIENT

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The clinical basis of this paper is a series of 44 intersex patients seen at the Research and Educational Hospitals and Clinics of the University of Illinois Medical School The study and care of these patients has always been a cooperative project involving many people, and I wish here to acknowledge my indebtedness particularly to Dr I P Bronstein, head of the Endocrine Clinic of the Pediatrics Department, as well as to Drs Ira Rosenthal, Elizabeth McGrew and many others who all worked together in the study and treatment of these patients The total number of patients is divided into groups as follows

True hermaphrodites	5
Male pseudohermaphrodites	11
Female pseudohermaphrodites	0
Adrenogenital syndrome	
females	22
males	9
Gonadal dysgenesis	5
Testicular hypoplasia	1
Total intersex	44

Approximately 20 years ago Dr Hugh H Young finished his book entitled GENITAL ABNORMALITIES, HERMAPHRODITISM AND RELATED ADRENAL DISEASES which was published in 1937 This is unquestionably the best book on the subject in English, or any other language It summarizes well all of the knowledge then available relating to this group of patients It is a landmark in the history of this subject and is still a most valuable source book for the history, basic anatomy, pathology, and clinical features of these conditions

There have been, however, a number of very important changes and additions to our knowledge in the intervening years Even the terminology is changing and the term, intersex is becoming more widely used rather than the old term, hermaphrodite The terminology is not yet rigidly fixed and in view of some of the changes we will mention later it would seem that an entirely new classification may have to be set up

Most fundamental is the change in the idea of what sex is and how it is determined Twenty years ago, sex was a fairly well defined state, which was determined by the histological nature of the gonads While some of the sexual characteristics were known to vary from the normal patterns, such variation could

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Read at annual meeting of American Association of Genito Urinary Surgeons, Osterville, Mass , June 4–6, 1956

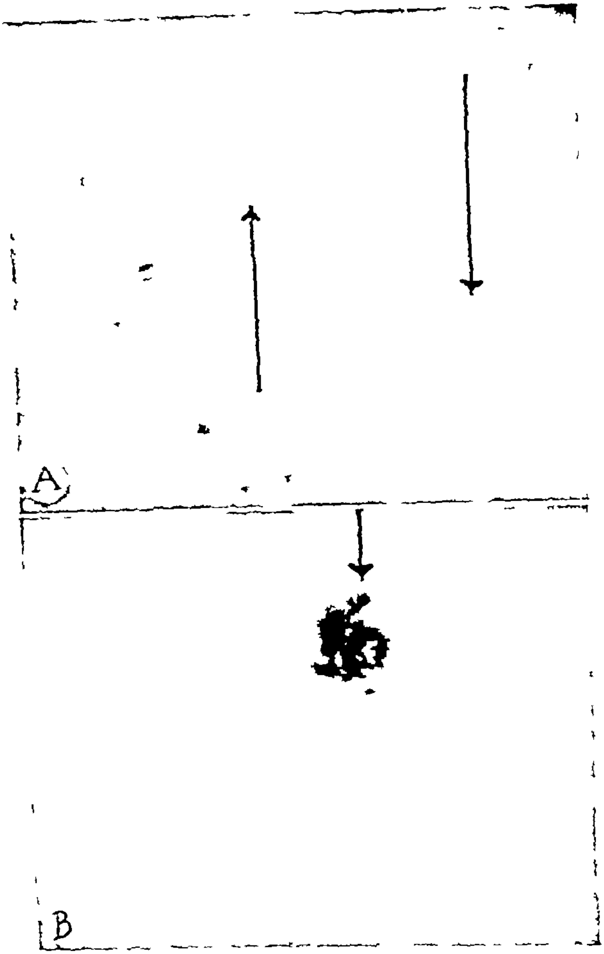

FIG 1 *A*, skin biopsy showing sex chromatin mass in several nuclei Case of adrenogenital syndrome Feulgen stain Oil immersion *B* oral mucosa smear showing sex chromatin mass in nucleus stained with crystal *echt* violet Oil immersion

other or as in so-called true hermaphrodites gonads of both types with either chromosomal pattern Gonadal type at this time can be determined only by biopsy and histologic section

The hormone pattern is now known to be a mixed one in every individual with a preponderance in either direction varying usually according to the gonadal type The exact role of the hormones elaborated by the fetal gonad in further sex differentiation and in development of the secondary sex characteristics has yet to be determined with certainty The general hormonal pattern can be determined by chemical tests and can be altered by administration of hormones

The character of the sex organs particularly the copulatory organs is increasingly important in the determination of the proper sex now that the gonadal and many lesser features, such as laryngeal development, voice, skin character, hair pattern, distribution of adipose tissue, etc

There is yet another factor determining sex, and that is the psychic pattern We know that this is influenced by the hormonal pattern as well as by the upbringing and experience of the individual However, we know that it is a very uncertain guide as to true sex, as proven by the many individuals with homosexual *tendencies*

After considering these factors which go into the determination of sex, we are in a little better position to define sex The definition we have evolved is not an exact one, but we think it states the situation as well as our present knowledge allows The definition is as follows Sex is the overall state of body and mind by which the individual conforms to the male or female standards of normality in the named sex-determining factors It is an algebraic summation of these factors in which no one factor supersedes the others In other words there is no single conclusive determining factor Every individual we know is a mixture of characteristics of the male and female, and it is the algebraic sum or preponderance of all these factors which determines sex, and not any single one of them

Discussing these factors individually we find that the greatest recent change has been in the study of the chromosomal pattern

The chromosomal pattern can now be determined quite accurately The method was discovered by Dr Murray L Barr of the University of Western Ontario in Canada about 1950 and was applied by him and his associates to determination of sex in intersex cases within the next couple of years Dr Barr has examined many skin biopsies for us and his method has been used by Dr Elizabeth McGrew at the University of Illinois with excellent results (fig 1, *A*) Accumulating experience confirms the accuracy of the method More recently, mouth (fig 1, *B*) (and vaginal) scrapings have been used and it seems that this method is just as accurate as the skin biopsy A group in England (Davidson et al) has also studied blood smears and they have detected a sexual difference in the nuclear pattern of the neutrophil leukocytes As a matter of fact the chromosomal pattern can be determined in the cells of many tissues provided they have been properly fixed Fixation with formalin tends to shrink the nuclei and clump the chromatin so that Dr Barr's method cannot be applied Tissues which have been fixed in Bouin's or Zenker's solutions, or the modified Davidson's solution recommended by Dr Barr for skin biopsies, will all give satisfactory sections for chromosomal study Mouth or vaginal scrapings are fixed as for exfoliated cell study in half and half ether and absolute alcohol Staining of tissue sections is done with H and E and Feulgen stain, while the mouth smears are stained with crystal *echt* violet The small chromatin mass is identified along the nuclear membrane in a majority of cells in females but in only a small percentage in males

The gonadal type is determined not only by the chromosome pattern but by separate genes which influence development of the gonad and thus it is possible for an individual to have a chromosome pattern of one sex and a gonad of the complicated element to the clinical picture Apparently the hyperplasia of the steroid-forming elements in some way alters the electrolyte-controlling hormone output so that there is sodium loss and retention of potassium This may lead to a clinical picture of shock, vomiting, dehydration, etc , which may place these patients, especially young infants, in a critical state The changes can be confirmed by chemical determination of the sodium and potassium levels in the serum

Diagnosis in adrenogenital syndrome is now simplified The finding of the female chromosome complex with an increased 24-hour output of 17-ketosteroids usually establishes the diagnosis The level of pregnanetriol output can also be done in questionable cases However, a therapeutic test with cortisone therapy, as introduced by Wilkins in 1950, will confirm the diagnosis if the 17-ketosteroid output drops If the 17-ketosteroid output does not drop the possibility of tumor of the adrenal cortex must be considered and further study done to rule this out

If the adrenogenital syndrome is accompanied by electrolyte disturbance the matter is one of more danger to life Cortisone therapy here also corrects the electrolyte disturbance, supplemented at first by DOCA (desoxycortico-sterone acetate) or percorten (long-acting) administration until the electrolyte levels are brought to more normal range Surgical treatment now is confined to resection of the enlarged clitoris and vulvoplasty to open the vagina Surgical resection of the adrenals is no longer necessary in the cases due to hyperplasia

In the case of adrenogenital syndrome due to tumor, surgical removal of the tumor is the only proper course Presacral retroperitoneal air insufflation is very helpful in these cases in making a diagnosis of adrenal tumor, also the lack of drop in hormone output with cortisone therapy We have had one such case with complete recovery following removal of the tumor

We should mention here that there have been reported a few cases in which there is apparently adrenocortical hyperplasia with electrolyte disturbance but without the adrenogenital syndrome In other words, the hormones produced are not androgenic so that no sexual effects of importance are noted In these cases hormonal treatment as just described corrects the electrolyte disturbance and is adequate treatment

The next largest group is that of so-called male pseudohermaphrodites In this group also there is frequent error in determination of sex at birth Many of these patients with hypospadias and undescended testis have been thought to be females and have been raised as such They usually require abdominal exploration for a complete diagnosis, however, if the gonads are in the groins, biopsy may be adequate in conjunction with cystoscopic and x-ray study of the internal genitalia Included in this group are individuals varying widely from those with a distinctly male habitus and hypospadias all the way to cases with a very female habitus, gynecomastia, a rudimentary penis and an almost normal size vagina Differential diagnosis must be made between this group and the so-called true hermaphrodites Most male pseudohermaphrodites have a gonadal and psychic pattern which is male and usually prefer to be male Usually their hormonal type is no longer the definite determinant As we all know there is a great variability even in normal persons, in the genitalia and secondary sex characteristics, but in many intersex cases the potential adaptability of the genitalia carries considerable weight in the determination and establishment of sex

There have been some very excellent recent studies of the psychic factors in the intersex group by Money and the Hampsons The psychologic study of very young children is a difficult matter, but these authors have examined a large number and have come to the conclusion that a person's ideas of his own sex or his "gender role," become fixed at a very early age, and that attempts to alter it by "change of sex" after early infancy are unwise We do not feel quite so strongly on this subject as they do We have had some examples of change of sex in later childhood and even teen age without disastrous consequence

As to the overall approach to the intersex patient, there are two basic principles First, the investigative workup should be done just as early in life as possible Second, on the basis of the findings, a prompt determination of sex should be made The final assignment of sex in any given individual is made only after group consideration and weighing of all the findings It is impossible to assign a fixed table of relative values to the various factors

The genitalia and secondary sex characteristics are not of primary biologic importance but we must remember that their character and development, especially of the copulatory organs, govern the potential adaptability of the individual to one or the other sex and therefore they assume a practical importance far above their biologic importance

The gonads are probably next most important The hormonal pattern is less important since it can be clinically altered at will with present day hormone preparations The psychic pattern is such an indefinite feature in infants and children that it carries much less weight than the organic factors in this group, but in the older child and adult it must be seriously considered

The chromosomal pattern is the most recent to be used and is in a sense the most basic factor biologically Still, it is not an entirely true guide in itself, as we see in those groups, previously mentioned, of gonadal dysgenesis and testicular hypoplasia

The final sex for the individual will be that which fits the gonadal, chromosomal, and genital sex patterns best In some cases, including the true hermaphrodites, where the genital organs are also indeterminate, the final decision will be most heavily influenced by the potential adaptability of the sex organs to the normal pattern of the sex selected This may be true even though it does not entirely agree with other factors

We shall now take up the individual groups and note the recent changes which have occurred The adrenogenital group is the largest and there has been a most profound change in the handling of these cases Many males are now found in this category although they are not classified as intersexes and do not concern us directly at this time In the last few years the discovery that some of these patients also have electrolyte disturbances has added another important and complicated element to the clinical picture Apparently the hyperplasia of the steroid-forming elements in some way alters the electrolyte-controlling hormone output so that there is sodium loss and retention of potassium This may lead to a clinical picture of shock, vomiting, dehydration etc , which may place these patients especially young infants, in a critical state The changes can be confirmed by chemical determination of the sodium and potassium levels in the serum

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Female pseudohermaphroditism of the non-adrenal group is the smallest group of all It is unusual to find a primary intersex with ovaries and we have not seen such a case Assignment of sex in such cases depends on the adaptability of the secondary sex organs and the correction necessary to adapt them to the assigned sex which is usually female

The most interesting group historically is that of the true hermaphrodites These cases have always been of exceptional interest and approximately sixty cases have now been well documented and reported By definition these individuals have both testis and ovarian tissue No case on record has ever had both testis and ovary functioning so as to form both fertile sperm and ova As a matter of fact, most intersex cases of all kinds are sterile The diagnostic problem in most of these is to determine the sex into which the patient best fits by the criteria aforementioned The established sex may or may not be in accord with the chromosomal pattern or with the apparent major gonadal element The secondary sex characters must be taken into consideration in considering the adaptability to the assigned sex Surgical correction can be accomplished quite satisfactorily in nearly all cases

The patients now called cases of gonadal dysgenesis were formerly known as ovarian agenesis or Turner's syndrome These individuals have completely undeveloped gonads and the genitalia and secondary sex characteristics are infantile female Recent sex chromosome studies reveal that most of them have a male chromosomal pattern, however, in the absence of any gonad whatsoever the female genital pattern develops, apparently by default, as it were This does not alter the clinical handling of these cases, they should continue as females, with hormone therapy to assist to this end

The group most recently added to the intersex fold is one made up of certain cases of testicular hypoplasia These patients present a clinical picture of gynecomastia, aspermatogenesis, but normal Leydig cell development The first case with hormonal studies was reported by Dr Bronstein of our group in 1939 In 1942 Klinefelter with others reported 9 cases and his name has since been connected with it Within recent months Dr Barr has shown that some of these patients have a female chromosomal pattern and we have had one patient in whom this pattern has been found (fig 2)

We are currently arranging to review our cases of hypoplasia of the testis seen during past years and expect to find others in that same situation

In conclusion we may emphasize again the following points First, the very idea of what constitutes an individual's sex has changed and whereas formerly the gonad type was thought to be the final determinant of sex, now it is felt that sex is the overall summation of many factors, namely, the chromosome pattern, gonad type, hormone pattern, sex organ pattern, and psychic pattern

These factors should be investigated as early as possible and the sex determined and established without delay

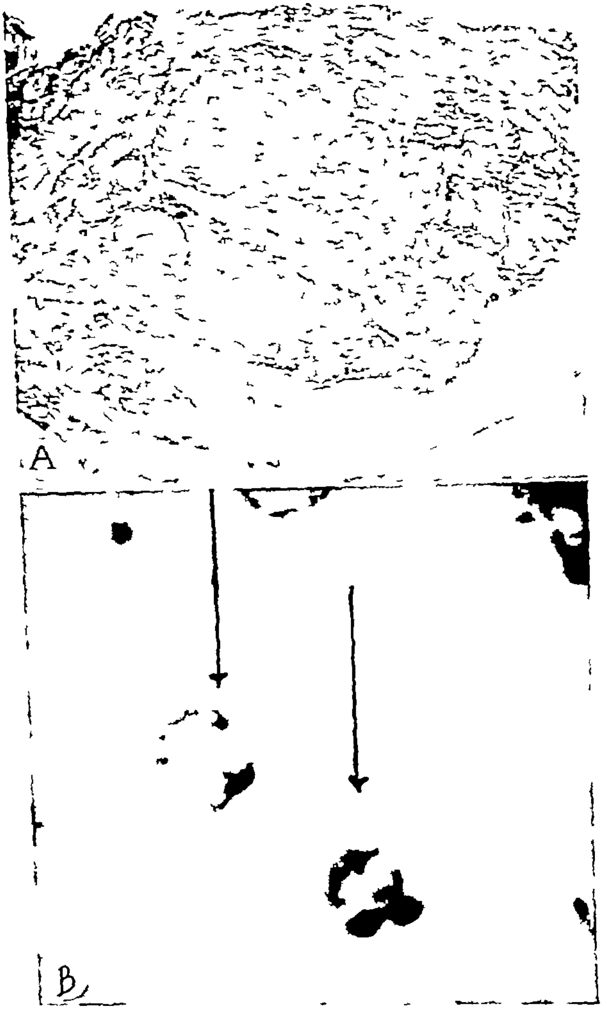

FIG 2 Biopsy of testis A case of testicular hypoplasia Hematoxylin and eosin stain Low power B case of testicular hypoplasia Hematoxylin and eosin stain Oil immersion showing sex chromatin mass in nuclei

The adrenogenital syndrome due to adrenocortical hyperactivity has been found to occur fairly often in males as well as females It is also found to be associated with an electrolyte disturbance characterized by loss of sodium which may lead to a serious electrolyte imbalance particularly in young infants Diagnosis of adrenogenital syndrome is now made on the basis of chromosome studies and hormone output surgical exploration being no longer necessary Treatment of adrenogenital syndrome is medical by administration of cortisone supplemented at first by DOCA in the early stages in those patients with salt-losing syndrome pattern is of the male type and correction of the situation usually involves hypospadias repair, orchiopexy and, in some cases, mastectomy

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THE ELECTROUROGRAM III EXPERIMENTAL WORK IN DOGS

ALFRED W KNEUCKER

From the Department of Surgery, Chicago Medical School, Chicago, Ill

This is the third of a series of papers on the Electrourogram In the first we showed its existence * The second communication, describing experiments on rabbits, demonstrated that each part of the kidney produces a specific curve † It was shown further that the curves of the renal parenchyma are entirely distinct from those of the hollow structures, i e pelvis and ureter ‡ It was also shown that the curves of the renal parenchyma are influenced by the action of diuretic and antidiuretic measures The present report deals with experimental work performed on dogs

TECHNIQUE

The experiments were performed under general anesthesia Nembutal intravenously, in doses of 10 mg per lb of body weight, was found to be the anesthetic of choice The volume of solution injected must be limited in order to avoid excessive diuresis from larger infusion which profoundly affects the curves Morphine or demerol premedication should not be used because they are antidiuretic

One of the major problems is the elimination of confusion from respiratory curves This can be accomplished in various ways

a) Some dogs breathe slowly and superficially under anesthesia These are ideal for the experiments but, unfortunately, they are very rarely encountered

b) Artificial respiration with a mechanical resuscitator is the principal method employed to deviate the curves produced by breathing Only pure oxygen should be used A tracheostomy should be performed and a Foley-type tracheal tube inserted This diminishes respiratory effort but does not completely abolish it

c) In order to eliminate it completely, phrenicotomy through the opened thorax may be performed However, in many animals, after a brief period of cessation, some respiratory movements are resumed

d) Tubocurarin, 0 1 mg per pound of body weight, slowly injected, is often helpful, but some animals react badly and succumb rapidly

e) Anectin (succinyl choline chloride) intravenously in 0 4 cc doses will stop the breathing for some time It may be repeated if necessary In our hands, mechanical respiration with tracheostomy and anectin gave the best results, and the complicating influence of the respiratory curve was almost negligible

The animals are starved for at least 8 hours before survery Immediately before the experiment starts, 50 to 100 cc physiological salt solution is administered subcutaneously to provide adequate diuresis

In dogs the right kidney usually lies just below the twelfth rib, whereas the left kidney is located a little lower in the retroperitoneal space It is, therefore,

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¶ Accepted for publication September 29, 1956

* J Urol 69 458 1953

† J Urol 75 250 1956

‡ Author has found out from many personal communications that the electrourogram has quite often been mistaken for the electroureterogram

Chromosomal type can now be quite easily determined by means of skin biopsy or oral and vaginal smears

Many cases of gonadal dysgenesis formerly thought to be female are now known to have a male chromosome pattern This has not altered the clinical treatment of these individuals

Some cases of testicular hypoplasia have been found to have a female chromosome pattern, however they still are to be treated as males

840 S Wood St, Chicago 12, Ill

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helpful to resect the twelfth rib on the right side The exposure of the organ is generally similar to that in human beings Care should be taken not to displace the kidney which might distort its circulation

A Sanborn Twin Viso apparatus* which permits the simultaneous registration of electric potentials from two organs (both kidneys, kidney and adrenal, kidney and ureter) was used in the experiments It should be mentioned that curves obtained through different techniques look different † A single channel machine in which the speed can be adjusted may also be used, however, registration of only one organ or one part of an organ at a time is often not satisfactory for experimental work

Either uni- or bipolar registration may be made After a considerable number of experiments in dogs and rabbits, the bipolar registration became the method of choice

As electrodes, needles are used, which can be introduced either superficially into the renal parenchyma to register the potentials from the cortex (electrofluorogram), or more deeply into the renal substance to register the potentials of the medulla (electromyelogram) If the needles do not snugly fit the metallic ends of the cable, adapters must be used ‡ If curves are registered percutaneously, as is the rule in man, § only the tips of the needles should conduct electricity, thus 3 to 5 mm of the needle remains uncovered while the rest is insulated, preferably with baked-on enamel ¶ The two needles inserted into the renal parenchyma represent the active electrodes for bipolar registration Other needles serve as inactive electrodes, they are inserted deeply into the adjacent muscles Concerning the leads there are the following possibilities

a) Unipolar registration In the rare cases where the registered curves are to be unipolar, the patient's cable which has 5 wires may be used in the following manner

Four inactive electrodes (needles) are inserted somewhere into the muscles, the active electrodes connected to the chest wire (colored brown) are inserted into the renal tissue If unipolar registration of both kidneys simultaneously is desired the one-wire cable, also colored brown, is connected to the needle which is thrust into the second kidney The machine has to be set on the V-lead after speed and sensitivity have been adjusted

b) If we want to register bipolar potentials from one kidney, which is the usual technique, we take the RA and LA wires (colored black and white, respectively), connect them to two needles inserted into the kidney and set the machine on Lead I The inactive electrodes, attached to the other three wires (red, green, brown), are placed as before, somewhere in the adjacent muscles

c) The Sanborn Company modified their Twin Viso apparatus for our purpose in the following way

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* Sanborn Company, Cambridge 39 Mass

† When, as it will be pointed out later the electrogastrogram was registered these curves differed considerably from the curves Goodman demonstrated in his work with the stomach See Goodman E N et al Gastroenterology, **29** 598 (October) 1955

‡ Manufactured by Sanborn Company

§ See EUG IV in this issue of J Urol, pp 543–548

¶ Such needles are manufactured by Cameron Surgical Specialty Company, 666 W Division St Chicago 10 Ill

The standard 3-wire input cable is connected to the AC amplifier jack on the Sanborn Twin Viso DC amplifier and recorder By this means the signals from the organ being measured are fed directly to the standard input circuit of the Sanborn electrocardiograph amplifier The white and the black wires represent the active electrodes, the green wire the inactive electrode Since we have two 3-wire input cables for the two channels of the Twin Viso machine, simultaneous bipolar records of both kidneys can be made, which is the ideal method of registration

The speed of the machine must be adjusted to the needs of the experiment For short examinations (and especially if the curves are to be studied as to whether they are influenced by action potentials from the heart or lungs, or in order to measure the distances between the peaks of the waves), the recommended speed is 5 mm / sec , or one-fifth of the regular speed of the electrocardiograph For long registration, as is the case with human beings, a speed 0 5 mm / sec is desirable

The question of sensitivity has not yet been answered The standard sensitivity of 1 mv = 10 mm on the paper is usually sufficient, but there are conditions under which an increased sensitivity, as for example 1 mv = 15 mm , seems to give better results

RESULTS

A) The following observations confirm beyond doubt that it is the renal parenchyma from which potentials are registered

1) If both ureters are exposed, severed from the bladder, and cannulated with vinyl tubes, the excreted urine is readily observed If curves from both kidneys are registered at the same time it becomes obvious that diuresis and writing are parallel * In addition, if the quantity of excreted urine is measured it will be seen that the larger the amount of excreted urine the higher are the amplitudes of the curve

2) If the diuresis is increased or if diuretics are administered, the amplitudes of the curves are increased, if antidiuretics are applied the amplitudes of the curves decrease If the renal pedicle is tied—which is a surgical antidiuretic measure—the curves flatten †

3) If the ureter is tied at the ureteropelvic junction the kidney stops working, accordingly the kidney stops writing The curves either fade out or change into curves from neighboring organs (see later, influence of curves on each other) The same is true if the ureteral cannula is blocked by a blood clot When the blood clot is removed and the urinary flow is restored, the kidney begins writing immediately, unless there is another reason for non-registration

4) Referring to the previously mentioned electrofiliogram and electromyelogram we see that shortly after diuresis has been induced the curves of the electrofiliogram have higher amplitudes than the electromyelogram, because the princi-

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* It takes some time for a drop of urine to travel from the renal papilla to the end of the cannula Therefore it may be that the kidney 'writes' and no urine seems to appear However a slight twist of the cannula or a different position of the kidney results in an immediate urinary flow

† This phenomenon was already mentioned in the EUG II

helpful to resect the twelfth rib on the right side The exposure of the organ is generally similar to that in human beings Care should be taken not to displace the kidney which might distort its circulation

A Sanborn Twin Viso apparatus* which permits the simultaneous registration of electric potentials from two organs (both kidneys, kidney and adrenal, kidney and ureter) was used in the experiments It should be mentioned that curves *obtained through different techniques look different* † A single channel machine in which the speed can be adjusted may also be used, however, registration of only one organ or one part of an organ at a time is often not satisfactory for experimental work

Either uni- or bipolar registration may be made After a considerable number of experiments in dogs and rabbits, the bipolar registration became the method of choice

As electrodes, needles are used, which can be introduced either superficially into the renal parenchyma to register the potentials from the cortex (electro-*fligram), or more deeply into the renal substance to register the* potentials of the medulla (electromyelogram) If the needles do not snugly fit the metallic ends of the cable, adapters must be used ‡ If curves are registered percutaneously, as is the rule in man, § only the tips of the needles should conduct electricity, thus 3 to 5 mm of the needle remains uncovered while the rest is insulated, preferably with baked-on enamel ¶ The two needles inserted into the renal parenchyma represent the active electrodes for bipolar registration Other needles serve as *inactive electrodes, they are inserted deeply into* the adjacent muscles Concerning the leads there are the following possibilities

a) Unipolar registration In the rare cases where the registered curves are to be unipolar, the patient's cable which has 5 wires may be used in the following manner

Four inactive electrodes (needles) are inserted somewhere into the muscles, the active electrodes connected to the chest wire (colored brown) are inserted into the renal tissue *If unipolar registration of both kidneys simultaneously* is desired the one-wire cable, also colored brown, is connected to the needle which is thrust into the second kidney The machine has to be set on the V-lead after speed and sensitivity have been adjusted

b) If we want to register bipolar potentials from one kidney, which is the usual technique, we take the RA and LA wires (colored black and white, respectively), connect *them to two needles inserted into the kidney and set the machine on* Lead I The inactive electrodes, attached to the other three wires (red, green, brown), are placed as before, somewhere in the adjacent muscles

c) The Sanborn Company modified their Twin Viso *apparatus for our* purpose in the following way

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* Sanborn Company, Cambridge 39, Mass

† When, as it will be pointed *out later* the electrogastrogram was registered these curves differed considerably from the curves Goodman demonstrated in his work with the stomach See Goodman E N, *et al* Gastroenterology, **29** 598 (October) 1955

‡ Manufactured by Sanborn Company

§ See EUG IV in this issue of J Urol, pp 543–548

¶ Such needles are manufactured by Cameron Surgical Specialty Company, 666 W Division St Chicago 10 Ill

The standard 3-wire input cable is connected to the AC amplifier jack on the Sanborn Twin Viso DC amplifier and recorder By this means the signals from the organ being measured are fed directly to the standard input circuit of the Sanborn electrocardiograph amplifier The white and the black wires represent the active electrodes the green wire the inactive electrode Since we have two 3-wire input cables for the two channels of the Twin Viso machine simultaneous bipolar records of both kidneys can be made which is the ideal method of registration

The speed of the machine must be adjusted to the needs of the experiment For short examinations (and especially if the curves are to be studied as to whether they are influenced by action potentials from the heart or lungs or in order to measure the distances between the peaks of the waves) the recommended speed is 5 mm / sec or one-fifth of the regular speed of the electrocardiograph For long registration as is the case with human beings, a speed 0 5 mm / sec is desirable

The question of sensitivity has not yet been answered The standard sensitivity of 1 mv = 10 mm on the paper is usually sufficient but there are conditions under which an increased sensitivity as for example 1 mv = 15 mm , seems to give better results

RESULTS

A) The following observations confirm beyond doubt that it is the renal parenchyma from which potentials are registered

1) If both ureters are exposed severed from the bladder and cannulated with vinyl tubes, the excreted urine is readily observed If curves from both kidneys are registered at the same time it becomes obvious that diuresis and writing are parallel * In addition, if the quantity of excreted urine is measured it will be seen that the larger the amount of excreted urine the higher are the amplitudes of the curve

2) If the diuresis is increased or if diuretics are administered the amplitudes of the curves are increased if antidiuretics are applied the amplitudes of the curves decrease If the renal pedicle is tied—which is a surgical antidiuretic measure—the curves flatten †

3) If the ureter is tied at the ureteropelvic junction the kidney stops working accordingly the kidney stops writing The curves either fade out or change into curves from neighboring organs (see later influence of curves on each other) The same is true if the ureteral cannula is blocked by a blood clot When the blood clot is removed and the urinary flow is restored the kidney begins writing immediately unless there is another reason for non-registration

4) Referring to the previously mentioned electrofiliogram and electromyelogram we see that shortly after diuresis has been induced the curves of the electrofiliogram have higher amplitudes than the electromyelogram because the princi-

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* It takes some time for a drop of urine to travel from the renal papilla to the end of the cannula Therefore it may be that the kidney writes and no urine seems to appear However a slight twist of the cannula or a different position of the kidney results in an immediate urinary flow

† This phenomenon was already mentioned in the ELG II

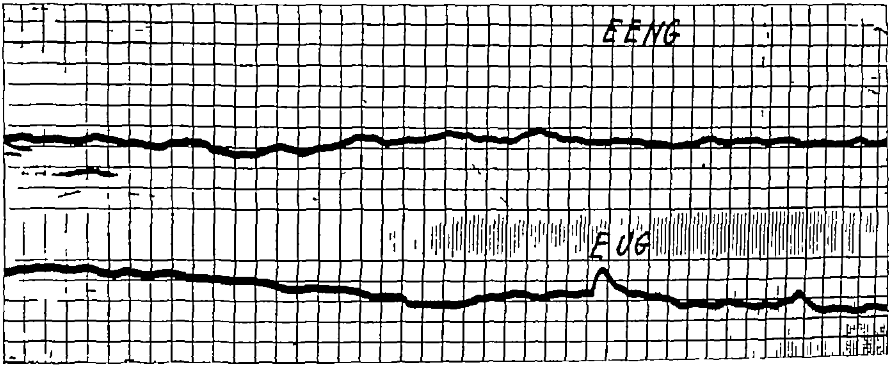

FIG 1 EENG = electroepinephrogram, EUG = electrourogram

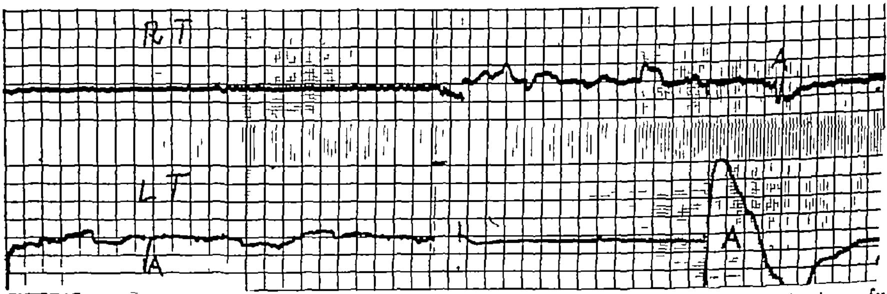

FIG 2 RT = right testicle, LT = left testicle, A = artefact In this registration, functions of testicles alternate

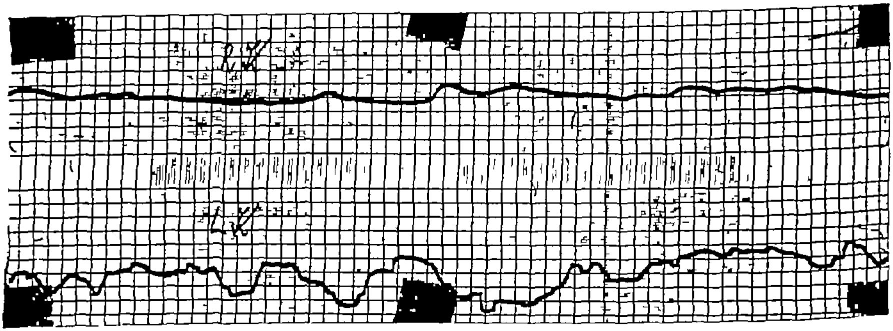

FIG 3 RK = right kidney, LK = left kidney

pal work of the kidney at that time is done by the cortex (glomeruli) About 10 minutes later, the medulla has to do the greater work and the curves of this part of the kidney (tubuli) show the higher amplitudes Still later, the curves of the renal pelvis and the ureter have the highest amplitudes *

5) The excised kidney which has neither circulation nor nervous impulses continues to write for 10 to 15 minutes (see EUG II) Parenthetically, the excised kidney keeps writing longer than any other excised parenchymatous organ, such as the liver

B) Tracings of organs of the same tract resemble each other Thus, the curves from the adrenals which are histogenetically akin to the kidneys, resemble

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* See EUG II

the renal curves (fig 1) If a kidney is removed and tracings are taken after the wound has properly healed, curves from the adrenal of the same side can be registered percutaneously These curves cannot be registered as long as the kidney is present For the reasons for this phenomenon see under E, 4

Finally, curves can be easily traced from the testicles, be it that the organ is exposed surgically, or that the curves are registered with needles inserted percutaneously, or taken with flat plates placed outside the scrotum over the testicles (electro-orchidogram, fig 2)* The testicular curves resemble the renal curves, too

C) As described in EUG II, the two kidneys often function alternately (fig 3) Concurrently, the amplitudes of the renal curves also alternate At a given time the left kidney, for instance, is more active than the right and, accordingly, the left kidney shows higher amplitudes Ten minutes later the right kidney is more active and the amplitudes of this kidney increase The same phenomenon can be observed very often when both testicles or both adrenals are registered simultaneously †

D) It may be that from one organ or, in rare cases, from both organs, no tracings can be recorded, although the machine is hooked up properly and there are no other technical errors ‡

E) Functional activity of neighboring organs exert a definite influence on the renal curves

1) Mention has been made above, and also in earlier reports, of the influence of respiration upon the renal curves

2) Similarly, the motion of the heart, the diaphragm, and the large vessels exerts an influence on the renal curves particularly during percutaneous registration of renal curves in human beings However, the spikes of the superimposed electrocardiogram are easily detected and can be avoided if the electrodes (needles) are either placed away from the large vessels (renal artery, aorta) or in the vicinity of such high vascularized organs as the kidney (pararenal) and not into the organ itself §

3) If the animal is fed a large meal just before the experiment starts, an electrogastrogram may be obtained

4) Potentials from the kidney suppress the registration of the adrenal curve in the living animal (electroepinephrogram = EENG) The larger organ is electrically more powerful Therefore, the larger kidney overcomes the potentials of the small adrenals as, under rare circumstances, the immense size and electrical strength of a full stomach overpower the renal curves

Therefore, it can be said that the electrical competition between organs depends upon the size or functional strength of the organs involved, their position in the neighborhood, and their movement It is sometimes difficult to exclude these influences in order to get the genuine, unaltered curve of an organ

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* In consequence but of no interest for the urologist electric potentials can be traced from all organs including the skin One is therefore, entitled to speak of Electrosplanchnography or Electrohistiography

† Figure 2 shows the curves from both kidneys taken simultaneously the left kidney is more active during the time of registration

‡ For reasons see EUG IV in this issue

§ See EUG IV pararenal position of needles in the human EUG In the animal experiment the needles may be inserted into the renal parenchyma and yet spikes from the electrocardiogram are seldom seen most likely since the kidney is dislocated and the circulation additionally changed somewhat on account of narcosis and surgery

SUMMARY

The nephron itself and its parts are the carriers and sources of renal potentials

Curves of organs of the same tract resemble each other

Curves can be registered from all organs

The function of paired organs and, accordingly, the height of the amplitudes of their curves, alternate

The curves usually influence each other, special ways had to be found to get pure curves from the organs under investigation

The technique of the experimental EUG in dogs is described in detail

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THE ELECTROUROGRAM IV THE ELECTRO-ORCHIDOGRAM, WORK IN MAN

ALFRED W KNEUCKER

From the Department of Surgery, Chicago Medical School, Chicago, Ill

The first three papers in this series reported the work done on animals This paper deals with the technique of the electrourogram (EUG) and electro-orchidogram (potentials from the male gonads) in human beings and some conclusions drawn from these investigations

TECHNIQUE

It was mentioned earlier that an EUG can be demonstrated in man * With one flat electrode placed on the surface of the body in the costovertebral angle and the other electrode in the form of a wire inside a ureteral catheter which is introduced into the kidney pelvis, we can take an EUG This type of tracing is usually not a true EUG, because it is confused with curves of the kidney pelvis Furthermore, there are two types of walls of the kidney pelvis, namely thin and thick ones, the thin ones do not exclude the electric potentials from the large vessels of the renal pedicle and, on the left side, from the aorta, as a result the EUG is often badly distorted by a modified electrocardiogram and the electropyelogram Therefore, new methods were sought for obtaining a pure EUG A successful technique is presented herewith

The patient lies in prone position, entirely relaxed, on a soft padded table or a cot equipped with a foam rubber mattress The mattress must be free of metal springs in order to exclude any metallic influence The quietly resting patient should avoid moving any part of the body, such as lifting his head, because such movements will show up as artefacts in the curves He breathes shallowly, if he takes a deep breath the respiratory curves will, at least partly, show up again If the patient holds his breath, which can be done only for a short time and not for the duration of the investigation, the kidney stops writing, at least in some individuals

The renal potentials are traced uninterruptedly for half an hour, because of the rhythm which makes the kidney stop working for periods of time † Should the patient want to move he has to inform the investigator and the machine must be stopped, after he has moved, the registration of curves may be resumed

Atropine and scopolamine may be administered to the patient in the usual doses, 20 minutes before the registration starts It is not absolutely necessary that these drugs be given, but they will have a calming effect on nervous patients Morphine and demerol, being antidiuretics, must be strictly avoided

For diuresis 500 to 750 cc of water should be taken before the registration The bladder should be emptied immediately before and after the recording so that the excreted urine can be measured and diuresis checked There are patients

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* The electrourogram J Urol 69 458, 1953

† See later

with greatly delayed diuresis, if, then, the patient fails to excrete urine there is small wonder that the kidneys do not produce electric potentials If there is the slightest doubt about possible residual urine, an indwelling catheter should be used

Again a Sanborn Twin Viso gave the best results in registering potentials from both kidneys simultaneously A single-channel machine can register the potentials from one kidney only and this is usually not sufficient The slight modification of the usual electrocardiograph described earlier in the EUG III was used in these investigations

The speed, with few exceptions, is set at 0 5 mm /sec when renal potentials are registered for 30 minutes * The standard sensitivity for human beings is usually 1 mv = 10 mm on the paper

Since the registration is bipolar two needles represent the active electrodes To spare the patient additional trauma, a suction cup as used in electrocardiography is utilized as the third inactive electrode The needles should fit snugly over the metallic ends of the cables If they do not, adapters are used The lead is standard

The needles, adequate for the weight and obesity of the patient, are 2½ or 3½ inches long, insulated with baked-on enamel, with the tips left uncovered for a length of 4 to 5 mm in order to pick up potentials only from the area into which they are inserted †

The question of the position of the needles is very important At the beginning of these experiments the needles were introduced into the renal parenchyma in the same manner as is done for renal biopsy or for measurement of intrarenal pressure However, this position of the needles very often resulted in spikes of a modified electrocardiogram superimposed over the EUG To get a true EUG it is much better to put the needles into the pararenal space, the kidney, being a heavy power plant, emits such strong potentials that they can easily be picked up from the adjacent area The skin and the underlying muscles in the renal area are pierced by the needles When resistance to the passage of the needles ceases, the loose fat of the pararenal space is reached and this is the correct place for the tip of the needle The needles should be placed away from the renal pedicle and in the area of the lower renal pole The two needles should be about one inch apart The inactive electrode, the suction cup, can be placed either on the buttocks or in the renal area in the vicinity of the needles The metallic parts of the electrodes must not touch each other

In some cases the electric potentials from the kidney are so strong that they can be traced by needles inserted hypodermically

For registration of electric potentials from the testicles (electro-orchidogram) needles should not be inserted since this causes unnecessary trauma to the testicles Instead, after the scrotum has been shaved, suction cups (because of the small size of the organ, infant suction cups are preferred) or flat electrodes are

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* See the Electrourogram III, pp 537–542

† For unipolar registration of one or both kidneys, or for registration with a single channel machine refer to The Electrourogram III, the only difference from canine investigation consists in the use of suction cups instead of needles for inactive electrodes

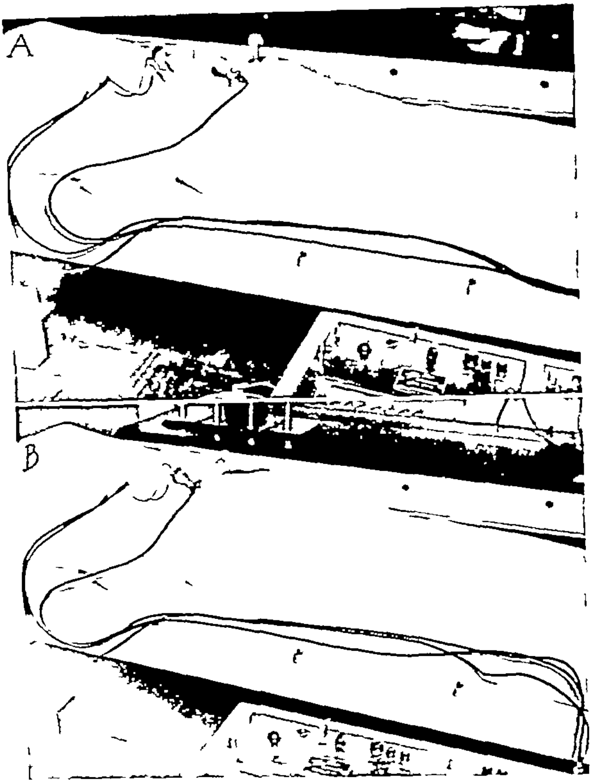

FIG 1 Arrangement of electrodes in human electrourogram *A*, inactive electrodes on buttocks *B*, inactive electrodes in renal area

placed on the surface of the scrotum just over the testicles As with the chest electrode of the electrocardiogram, the patient himself may hold the suction cups firmly in place without touching the metallic parts of the electrodes Potentials can be registered from either testicle separately or from both testicles together Again, the three-wire cable in standard position is the optimal for registration, since the examination is bipolar The inactive electrode can be placed either on one of the adjacent muscles of the abdomen or the thigh, but not over the area of the femoral vessels

The attached pictures show the arrangement of the electrodes for registration of the EUG and the electro-orchidogram (figs 1 and 2)

RESULTS

It occasionally happens that no potentials can be traced either from the kidneys or from the testicles The reasons may be the following

1) Failures of the machine

There is no current The main cable is broken, fuses are blown There may be defects of the patient's cable, the writing stylus, or other defects in the electronic equipment

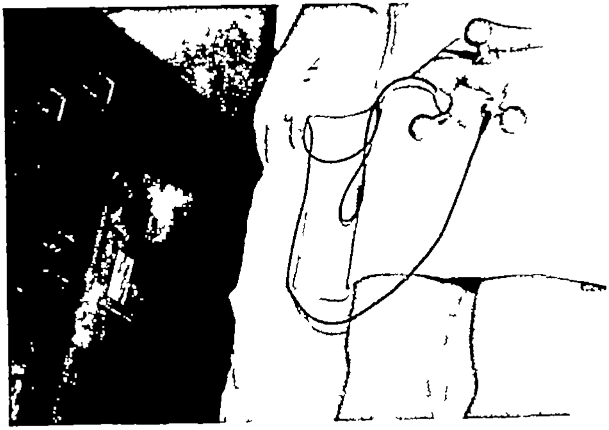

FIG 2 Arrangement of electrodes in electro orchidogram

The wrong leads may be used The centering of the stylus or its sensitivity may be wrong In addition, sometimes AC may disturb the curves

2) Somatic disturbances on the part of the patient This is not the place to discuss these The whole topic is now under investigation

3) Some patients show an accelerated or delayed diuresis In some individuals the diuresis occurs precipitously within the first minutes after the intake of water, while in others it is delayed for 30 to 60 minutes Nervous influences probably play a dominant role in such cases Therefore, as was explained earlier, it is very important to measure the amount of excreted urine before and after registration, further, the registration of the curves should begin immediately after the intake of the water to detect a possible precipitous excretion

4) Investigators tracing electric potentials from the human skin described a strange rhythm in the functional activity of this organ Regelsberger,* discussing this rhythm, mentions the following experiment on the kidney Even the strongest parenterally injected diuretic, for example novasurol, a diuretic of the mercury group, fails to produce an excretion of urine if function is counteracted by the rhythm †

According to Regelsberger, the rhythm itself seems to depend upon a central nervous impulse originating in the hypothalamic region, the center of diuresis, and influencing the membrane of each renal cell Therefore, the arrangement of negative ions just inside the cell membrane and the positive ions outside the cell membrane may not be enough to produce a current The migration of ions though the membrane depends upon a central nervous impulse, hence, for the production of an electric current the aforementioned arrangement of ions plus a central nervous impulse may be needed This impulse is neither permanent nor regular, which is the reason for the rhythm in the activity of organs However, the "rhythm" as described by Regelsberger, and the impulse from the hypothalamus is not in all cases responsible for the functional activity and inactivity of the organ

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* See Regelsberger, H , Der bedingte Reflex und die vegetative Rhythmik des Menschen- dargestellt am Elektrodermatogramm (The Conditioned Reflex and the Vegetative Rhythm of Man as displayed in the Electrodermatogram) Vienna Springer Verlag, 1952

† P 144 of the book just quoted

a) Excised kidneys write for quite a time after nephrectomy, usually about 7 minutes One could imagine that the impulse just present before nephrectomy may continue and influence the renal activity, although this is not too likely

b) The fact that potentials can be traced from tissue cultures where there is no hypothalamus to emit an impulse, is proof enough that the electric activities do not depend on nervous impulses from the midbrain alone Even in tissue cultures activity and inactivity phases change continuously with the result that real curves alternate with flat lines Without strictly denying Regelsberger's ideas, it seems that cells carry on discontinuous electrical activities the potentials of which may be registered discontinuously, too

5) Therefore, it is possible that the kidney being examined may not work for some time Hence it is preferable to register the activities of both kidneys simultaneously, since it may be

a) that the kidney under investigation does not work whereas the opposite organ produces potentials at that time or

b) that both kidneys stop writing for some time, although this rarely happens The same holds true for the testicles and the adrenals

To overcome the discontinuous activity and with it, the pause in registration, it is recommended that potentials from these organs be traced for at least half an hour If the kidney does not write, the curves either fade out or go over into one from some influencing organs in the neighborhood, usually the respiratory curve Conversely, if the respiratory curve appears in spite of the patient's shallow breathing, it may be concluded that the discontinuous electrical activity has caused the kidney to stop working After a period of registration of the respiratory curve the genuine renal parenchyma curve suddenly reappears

6) In man also, there is the alternation of function which was found in animals, and with it, the height of the amplitudes of the registered curves alternates between the two organs In rare cases, however the function of both kidneys is equal and the amplitudes of either curve are almost equal to each other

It can be said with confidence that the tracing of curves from the renal parenchyma is simple and without danger Actually, nothing worse happens to the patient than the insertion of two No 18 needles just beyond the muscles into the pararenal area Thus, less trauma is done to the body than by an intramuscular injection The preparation for the EUG is very simple and the investigation is less disagreeable for the patient and much easier for him to bear than are the usual urologic instrumentations The technique of the electro-orchidogram is extremely simple Even the slightest pain is spared the patient by the use of suction cups

Although the technique described here has proved to be satisfactory it is nevertheless possible that after our knowledge of the EUG and electro-orchidogram has increased, improved methods may be developed in the future

SUMMARY

The exact technique of the EUG and the electro-orchidogram in human beings is described, and it is pointed out that the investigation is neither dangerous nor unpleasant for the patient About 100 tracings of kidneys as well as of testicles have been taken which give promise of providing new avenues for research in human renal and testicular physiology and disease

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AN INEXPENSIVE INFALLIBLE TIDAL IRRIGATOR

JACK LAPIDES, SHELDON L FELLMAN AND JOHN R BELJAN

From the Section of Urology, Department of Surgery, University of Michigan Medical School, Ann Arbor, Mich

On occasion the physician finds it necessary to irrigate or to distend intermittently a patient's bladder over a prolonged period of time Periodic instillation of fluid into the bladder is tedious and time-consuming when done manually For this reason various tidal irrigators, utilizing the principle of the hydraulic siphon, have been devised to perform the task automatically In the past the many types of tidal irrigators used at the University of Michigan Medical Center were found to be inconstant and unreliable in their performance, other clinics have had similar experiences In fact, the problem has been so vexing that it stimulated an analysis by a hydraulics engineer[1] of the principles involved in tidal irrigation

Recently however, an apparatus (similar to one depicted by Stone[2]) has been devised which always works and is easy to construct from a simple, inexpensive drainage irrigator The basic unit is the Keyes drainage irrigator[3] (fig 1) which is used routinely on our wards for most urinary drainage In order to convert the Keyes device to tidal drainage, two modifications are necessary

The first step involves the insertion of an air valve into the system for the purpose of interrupting the siphon after the bladder has been emptied The air valve can be made by attaching a length of rubber tubing to the free limb of the glass Y tube closest to the drainage bottle (fig 2) The upper end of the rubber tube is clamped completely airtight A No 24 gauge hypodermic needle is then thrust into the lumen of the rubber tube just below the clamp

The second step concerns the siphon tube which is formed by simply elevating a portion of the tube running from the glass Y to the drainage bottle, it is raised above the level of the bladder so as to form an inverted U (fig 3) The siphon tube can be composed either of rubber or plastic It should be long enough so that the inverted U portion can be raised to any desired height *The most important point about the siphon tube is its inside diameter which must be 3/16 inch or 5 mm* Incomplete emptying of the bladder will occur if the diameter of the tubing is larger, since good siphonage will not be obtained If the diameter of the siphon tube is too small, siphonage will be continuous (once it has started) without the occurrence of further filling of the bladder Other investigators[2, 4, 5]

Read at annual meeting, North Central Section of American Urological Association, Cleveland Ohio, October 3–5, 1956

[1] Miller, W M Tidal drainage analysis Trend in engineering Publication Univ of Wash, 5 5–7, 1953

[2] Stone E B Functional evolution of the neurogenic bladder in paraplegic patients J Urol, 63 682, 1950

[3] Nesbit, R M Transurethral Prostatectomy Springfield, Ill Charles Thomas, 1943, p 52

[4] Cone, W V and Bridgers, W H A combined tidal irrigator and cystometer for management of the paralyzed bladder Surg, Gynec & Obst, 75 61, 1942

[5] Rupel, E and Culbertson C G A simple automatic bladder irrigator J Urol 50 446 1943

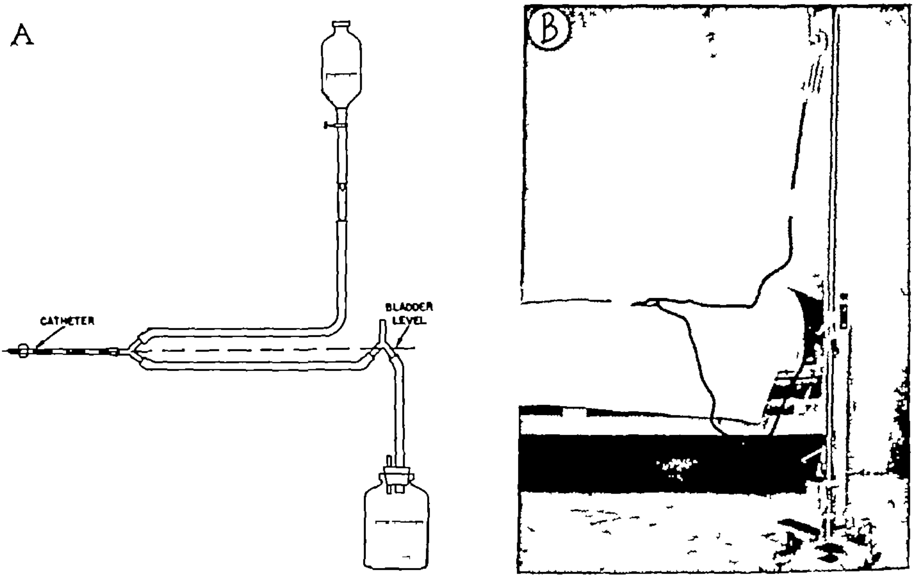

FIG 1 Keyes drainage irrigator *A*, diagram of components of irrigator *B*, photograph of device used clinically Observe calibrated irrigating bottle, clamp, Murphy drip, glass Y tubes and drainage bottle

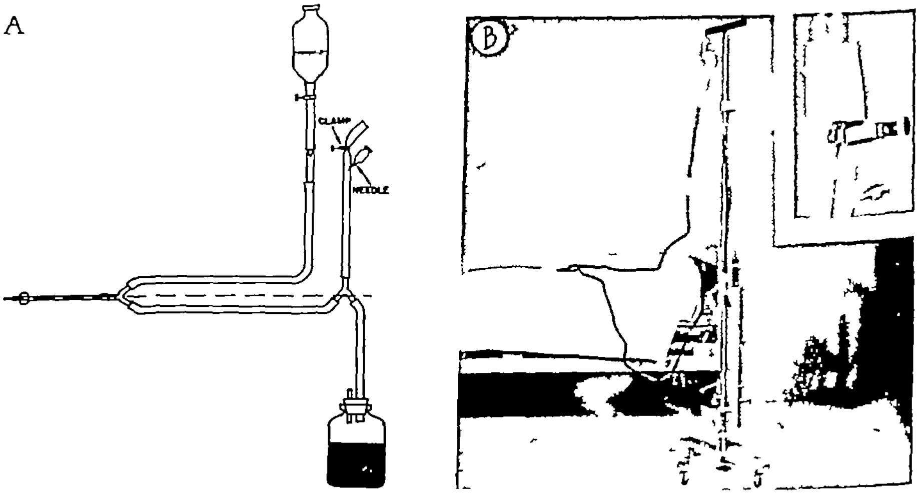

FIG 2 Initial step in conversion of Keyes device to tidal irrigator *A*, diagram of air valve construction Rubber tube fitted on free limb of glass Y tube at foot of bed, end is clamped airtight and No 24 hypodermic needle inserted into lumen of rubber tube just below clamp *B*, photograph of added air valve with closeup of needle air inlet

have recognized the critical importance of the inside diameter of the siphon tube The U portion of the siphon tube must never be raised as high as the needle of the air valve

It should be emphasized that the glass Y to which the air valve and siphon tube are connected should be placed at the level of the patient's bladder In

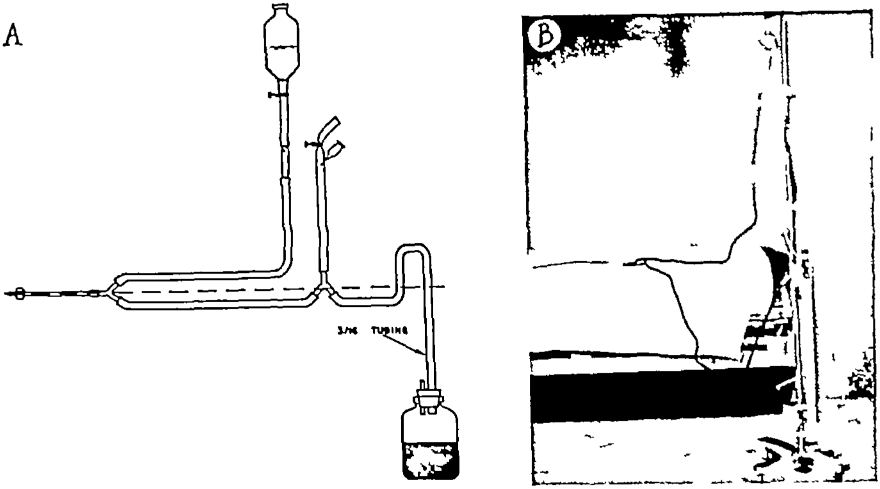

FIG 3 Final step in conversion of drainage apparatus to tidal irrigator *A*, diagram of formation of siphon tube Note that this is accomplished by simply raising portion of plastic tubing going to collection bottle, above level of bladder *B*, photograph illustrates finished tidal irrigator Various components are held in place by adhesive tape

actual practice the glass Y connector, air valve and siphon tube are all attached by adhesive tape to the upright holding the irrigating flask

It will be noted that a device for measuring intravesical pressure has not been included in the apparatus Bladder volume and not intravesical pressure is the significant factor in either irrigation or intermittent distension of the viscus The intravesical pressure gives the physician no idea of the bladder volume *The particular volume to which one desires the bladder to be filled before it is emptied by the hydraulic siphon must be ascertained through trial and error, i e, by varying the height of the siphon tube above the level of the bladder and then measuring the amount of fluid siphoned from the bladder with each variation* The frequency of bladder emptying will depend upon the rate of instillation of irrigating fluid as well as the height of the siphon tube

The tidal irrigator described in this paper has been used in large atonic as well as small spastic bladders and has been found to be completely satisfactory

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PROGRAM, ANNUAL MEETING OF AMERICAN UROLOGICAL ASSOCIATION, MAY 6–9, 1957, HOTEL PENN-SHERATON, PITTSBURGH, PA

Monday, May 6

Scientific Sessions 9 15 a m to 12 noon

Complete Replacement of Both Ureters by an Ileal Loop D M Davis and T F Nealton, Jr , Philadelphia, Pa

Total Ureteral Replacement with Small Intestine Technique and Results Hardy Ulm, New York, N Y

Urologic Complications Resulting from Use of Radioactive Gold in Treatment of Carcinoma of the Uterus M R Carlin, St Louis, Mo
Discussion R H Flocks, Iowa City, Iowa

Sterile Fluoroscopy Preliminary Report of New Technique for Localization of Renal Calculi A M Baskin, A H Janzen and B M Harvard, New Haven, Conn

Recognition and Management of Trauma to Kidney J R Liska, Greensburg, Pa
Discussion A H Wood, Baltimore, Md

The Healing of Renal Wounds I Partial Nephrectomy J J Murphy and Richard Best, Philadelphia, Pa

Ileocystostomy for Neurogenic Bladder J J Cordonnier, St Louis, Mo
Discussion J W Merricks, Chicago, Ill

Functional Analysis of the Bladder after Ileocystoplasty S R Weinberg, T J Sinatra and G Vasquez, Brooklyn, N Y

Tuesday, May 7

Motion Pictures 8 00 a m to 9 00 a m

Plastic Repair of Circumcaval Ureter R C Bunts, Richmond, Va

Nephroureterectomy For Reduplication of Kidney and Ureter Lt Col Kryder Van Buskirk, Washington, D C

Thoracico Lumbar Nephrectomy F P DeRosa, Chicago, Ill

Scientific Sessions 9 00 a m to 12 30 p m

Diseases of the Prostate F K Mostofi, Washington, D C

Symposium on the Kidney Renal Transplantation, Hypertension and Renal Vascular Surgery J H Harrison, Boston, Mass , Moderator

Some Aspects of the Comparative Anatomy and Physiology of the Kidney Allan L Grafflin, Baltimore, Md

Transplantation of Kidneys in Identical Twins J E Murray and J H Harrison, Boston, Mass

Diagnosis and Surgical Treatment of Diseases of the Renal Artery E F Poutasse and W J Engel, Cleveland, Ohio

After presentation of the foregoing three papers, a question and answer period will follow

Motion Pictures 2 00 p m to 5 00 p m

Thoracico Lumbar Excision of Adrenal Tumor Hardy Ulm and Sheldon Rudansky, New York, N Y

Adrenalectomy J H Harrison, Boston, Mass

Operative Technique for Cystectomy and Ileal Loop Urinary Diversion W F Leadbetter and V A Politano Boston, Mass

Ileocystoplasty W E Goodwin, Los Angeles, Calif

Construction of Ileocecal Bladder J W Merricks, Chicago, Ill

Retropubic "Saucerization" Operation for Cyst of Utricle H M Spence Dallas Texas

The Radioactive Diodrast Renogram C C Winter Los Angeles, Calif

Renal Transplantation B F Miller, Boston, Mass

Wednesday May 8

Motion Pictures 8 00 a.m to 9 00 a m

Repair of Hypospadias with Herniation of Bladder E A Slotkin, Buffalo, N Y

Radical Nephrectomy with Dorso-Lumbar Flap Incision G R Nagamatsu and A L Dean, New York N Y

Excision of Diverticulum of Renal Pelvis Gilbert Ottenberg, L G Lewis and R E Byrne, Washington, D C

Pathologic Changes in the Urinary Tract Demonstrated by X-Ray Motion Pictures J A Benjamin Rochester, N Y

Scientific Sessions 9 00 a m to 12 30 p m

The Steroids W P Herbst Washington, D C

Hypospadias The Principle of the Third Degree H T Thompson and Warren George, Rochester, N Y
Discussion R M Nesbit Ann Arbor, Mich

Effects of Antibiotics and Vaccination in Experimental Pyelonephritis H M Weyrauch, M L Rosenberg and Arjan Amar San Francisco Calif
Discussion Grayson Carroll St Louis Mo

Radical Excision of Locally Extensive Carcinoma of Deep Male Urethra V F Marshall New York, N Y
Discussion M H Nourse

Median Bar Uses and Abuses of Transurethral Resection Terence Millin, London England

Obstruction of Both Ureters by Retroperitoneal Inflammation H S Talbot and Edward Mahoney, West Roxbury Mass
Discussion T D Moore Memphis Tenn

Cinepyelography in Clinical Urology H G Hanley London England

The Standardized Columbia University Cystogram J K Lattimer A L Dean Jr and C B McCoy New York N Y
Discussion C M Stewart Los Angeles Calif

Cytochemical Studies of Prostatic Epithelium Lester Persky Rudolf Leuchtenberger and Cecilie Leuchtenberger Cleveland Ohio

2 00 p.m to 3 30 p.m

President's Address The Human Side of Medicine C H deT Shivers Atlantic City N J

Ramon Guiteras Lecture Use of Segments of the Small and the Large Intestine in Urological Surgery, with Special Reference to the Problem of Ureterocolic Anastomosis L N Pyrah, Professor of Urological Surgery at the University of Leeds, England

Thursday, May 9

Motion Pictures 8 30 a m to 9 30 a m

Parasacral Prostatectomy B S Vallett, Wilmington, Del

Radical Perineal Prostatectomy Reginald A Hancock, Pittsburgh, Pa

Repair of Vesico Rectal Fistula W E Goodwin, Los Angeles, Calif

Scientific Sessions 9 30 a m to 12 30 p m

Parasacral Prostatectomy, First Impressions B S Vallett, Wilmington, Del

Unilateral Renal Disease and Hypertension (Prize Essay) C C Winter, Los Angeles, Calif

Panel Discussion Undergraduate Training in Urology Moderator, C C Higgins, Cleveland, Ohio Collaborators Edgar Burns, New Orleans, La , G F Cahill, New York, N Y O W Hyman, Dean of the Medical School of the University of Tennessee, Memphis, Tenn , and G M Piersol, Dean of the Graduate School, the University of Pennsylvania, Philadelphia

The Behavior of Certain Metastatic Malignant Diseases Arising in the Urinary Tract R M Bobbitt, I F Harwood and F M Peck, Huntington, W Va
Discussion Samuel A Vest, Charlottesville, Va

2 00–5 00 p m

Ureteral Regeneration, Experimental and Clinical, Part III R G Weaver, Salt Lake City, Utah
Discussion F C Hamm, Brooklyn, N Y

An Operative Technique for Correction of Reflux V A Politano and W F Leadbetter, Boston, Mass
Discussion R C Bunts, Richmond, Va

Renal Acidosis and Uremia in the Newborn Due to Unrecognized Bladder Neck Obstruction W F Melick and J J Naryka, St Louis, Mo
Discussion H M Spence, Dallas, Texas

Indications for Nephrectomy, Nephroureterectomy, Partial Nephrectomy or Speleotomy in Renal Tuberculosis Einar Ljunggren, Goteborg, Sweden

Treatment of Urethritis in the Female Charles Eberhart, Atlanta, Ga
Discussion N B Powell, Houston Texas

Selective Sacral Neurectomy in Interstitial Cystitis W B Garlick and W A Milner, Albany, N Y
Discussion C F Schroeder Detroit, Mich

Induction of Incoming President, William J Baker

TECHNICAL EXHIBITS

Mr William P Didusch, *Director*

Name and Address of Firm	Booth Number
The Ambutainer Co , New York N Y	49
American Cystoscope Makers, Inc , New York, N Y	27 28, 29, 30, 31, 32, 33, 34

American Sterilizer Co., Erie, Pa.	16
Ames Co. Inc., Elkhart, Ind.	10
Ayerst Laboratories, New York, N. Y.	45
C. R. Bard, Inc., Summit, N. J.	38, 39, 40
The Coca Cola Co., Atlanta, Ga.	1
The Columbus Pharmacal Co., Columbus, O.	6
Cutter Laboratories, Berkeley, Calif.	37
Eaton Laboratories, Norwich, N. Y.	23, 24
Feick Bros. Co., Pittsburgh, Pa.	14
Greenwald Surgical Co. Inc., East Gary, Ind.	9
Grune & Stratton, Inc., New York, N. Y.	7
Guardian Chemical Corp., Long Island City, N. Y.	4
Hoffmann La Roche, Inc., Nutley, N. J.	25
Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.	21
Liebel Flarsheim Co., Cincinnati, O.	42, 43
Mallinckrodt Chemical Works, St. Louis, Mo.	17, 18
Metro Medical Distributors, Inc., Brooklyn, N. Y.	22
The Wm. S. Merrell Co., Cincinnati, O.	36
V. Mueller & Co., Chicago, Ill.	19
National Electric Instrument Co. Inc., Elmhurst, N. Y.	2, 3
Nepera Chemical Co. Inc., Yonkers, N. Y.	44
Parke, Davis & Co., Detroit, Mich.	35
Pfizer Laboratories, Brooklyn, N. Y.	11
Picker X-ray Corp., White Plains, N. Y.	15
Radium Chemical Co. Inc., New York, N. Y.	48
Radium Emanation Corp., New York, N. Y.	41
J. B. Roerig & Co., Chicago, Ill.	50
Charles A. Schmidt Instrument Co., St. Louis, Mo.	5
Smith, Kline & French Laboratories, Philadelphia, Pa.	12
E. R. Squibb & Sons, New York, N. Y.	8
The Stuart Co., Chicago, Ill.	13
The Williams & Wilkins Co., Baltimore, Md.	26
Winthrop Laboratories, New York, N. Y.	46, 47

SCIENTIFIC EXHIBITS*

Dr. Samuel A. Vest, *Chairman*

Effects of Antibiotics and Vaccination in Experimental Pyelonephritis. A. D. Amar, M. L. Rosenberg and H. M. Weyrauch, San Francisco, Calif.

Some Contributions of Dr. Hugh H. Young to Operative Urology. Armed Forces Institute of Pathology (for the Instrument Collection Committee of the American Urological Association), Washington, D. C.

Avulsions of the Male Genitalia. D. A. Culp, W. C. Huffman and R. H. Flocks, Iowa City, Iowa.

Ureteral Stones. A Record of the Development of Instrumental Treatment, Preferred Operative Treatment and Analysis of Stone by Petrocystallography. W. M. Coppridge, L. C. Roberts and Jack Hughes, Durham, N. C.

Wirt B. Dakin Historical Museum of the American Urological Association. W. B. Dakin, Los Angeles, Calif.

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* As of February 15, 1957. *Editor.*

Program continued on page 556

Uroflometric Observations of Women Walter Peter and W M Drake, Jr , Camden, N J

The Horseshoe Kidney T R Fetter, N R Varano and Robert Ayres, Philadelphia, Pa

Chyluria R A Hancock, Pittsburgh, Pa

Sex Chromatin in Sexual Anomalies J H Kiefer, Ira Rosenthal, Elizabeth McGrew and I Pat Bronstein, Chicago, Ill

The Electrourogram A W Kneucker, Chicago, Ill

Infallible Tidal Irrigator Urinary Ileostomy Device Jack Lapides, S L Fellman, J R Beljan and R E Boyd, Ann Arbor, Mich

Male Infertility Irving Maisel, Newark, N J

An Automatic Recording Cystometer D F Milam, Charleston, W Va

An Operative Technique for Correction of Reflux V A Politano and W F Leadbetter, Boston, Mass

Renal Angiography Indications and Experience with a Safe Technique E F Poutasse, W J Engel and H J Klapproth, Cleveland, O

Radioactive Zinc in the Male Canine Genitalia G R Prout, Michael Sierp and W F Whitmore, Jr , New York, N Y

Experiences with Six Opaque Media in Intravenous Urography (Five Thousand Case Studies) H R Trattner, Albert Flores, G S Krishnamurti and Fuad Boulos, Cleveland, O

Renal Disease and Hypertension Radioactive Diodrast Renogram as a Screening Test C C Winter, Los Angeles, Calif

Urinary Bladder Substitutes Experimental Study A E Goldstein, B S Abeshouse, Cafer Yildiran, Morton Goldfarb and R B Goldstein, Baltimore, Md

The Baylor Plan for Undergraduate Teaching of Urology A J Leader, Houston, Texas

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RENAL PAPILLARY NECROSIS: A CLINICOPATHOLOGIC STUDY OF 42 CASES*

HOWARD B. SIMON, WARREN A. BENNETT AND JOHN L. EMMETT

From the Section of Urology and the Section of Pathologic Anatomy, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Acute necrosis of the renal pyramids is a relatively uncommon clinicopathologic entity. It was first described in 1877[1] but not until Günther[2] (in 1937) emphasized the association of diabetes mellitus with papillary necrosis did additional exhaustive reports appear. To January 1, 1955, 211 cases had been reported. In the vast majority the associated condition was either diabetes mellitus (129 cases) or obstruction of the urinary tract (76 cases). The latter occurred principally among nondiabetic patients (59 of 82 cases).

Many different factors have been said to be of pathogenetic importance in renal papillary necrosis. The normally poor blood supply of the pyramids as compared with that of the rest of the kidney has been referred to often.[2, 3] Similarly, compression of the pyramidal blood vessels by inflammatory exudate in the presence of acute pyelonephritis or by para-amyloid deposition and increased intrapelvic pressure caused by urinary obstruction or retrograde pyelography frequently have been implicated.[1, 5, 8-11] Currently the most common theory holds that the condition has a basis in compression of pyramidal blood vessels by inflammatory exudate, particularly in diabetic persons, and by increased intrapelvic pressure caused by obstruction of the urinary tract. Both these actions serve to deplete further the pyramidal blood supply, which normally is not abundant.

Papillary necrosis has been produced experimentally in nondiabetic animals by ureteral ligation and the concomitant intravenous injection of colon bacilli.[12]

Accepted for publication October 15, 1956.

* Abridgment of thesis submitted by Dr. Simon to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Urology.

[1] Friedreich, N.: Ueber Necrose der Nierenpapillen bei Hydronephrose. Arch. path. Anat., 69: 308-312, 1877.

Günther, G. W.: Die Papillennekrosen der Niere bei Diabetes. München. med. Wchnschr., 84: 1695-1699, 1937.

[3] Edmondson, H. A., Martin, Helen E. and Evans, Newton: Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus. Arch. Int. Med., 79: 148-175, 1947.

[4] Robbins, S. L., Mallory, G. K. and Kinney, T. D.: Necrotizing renal papillitis: A form of acute pyelonephritis. New Eng. J. Med., 235: 885-893, 1946.

[5] Mellgren, Jan and Redell, Gunnar: Zur Pathologie und Klinik der Papillitis necroticans renalis. Acta chir. scandinav., 84: 439-457, 1941.

[6] Robbins, E. D. and Angrist, Alfred: Necrosis of renal papillae. Ann. Int. Med., 31: 773-793, 1949.

Gunther, G. W.: Die Mark- und Papillennekrosen der Niere, Pyelonephritis und Diabetes. Ztschr. Urol., 41: 310-344, 1948.

[8] Knutsen, Arne, Jennings, E. R., Brines, O. A. and Axelrod, Arnold: Renal papillary necrosis. Am. J. Clin. Path., 22: 327-336, 1952.

[9] Mandel, E. E.: Renal medullary necrosis. Am. J. Med., 13: 322-327, 1952.

[10] Muirhead, E. E., Vanatta, J. and Grollman, Arthur: Papillary necrosis of the kidney: A clinical and experimental correlation. J.A.M.A., 142: 627-631, 1950.

[11] Mandel, E. E. and Popper, Hans: Experimental medullary necrosis of the kidney: A morphologic and functional study. A.M.A. Arch. Path., 52: 1-17, 1951.

[12] Mallory, G. K., Crane, A. R. and Edwards, J. E.: Pathology of acute and of healed experimental pyelonephritis. Arch. Path., 30: 330-347, 1940.

TABLE 1 *Distribution according to age and sex 42 cases of renal papillary necrosis*

Age (years)	Patients		Sex	Patients*	
	Nondiabetic	Diabetic		Nondiabetic	Diabetic
0– 9	1		Male	21	3
10–19	1		Female	9	4
20–29	4				
30–39	0	1			
40–49	8				
50–59	6	2			
60–69	7	1			
70–79	4	3			
80–89	4				

* There were 42 patients but the status of diabetes was undetermined in five

TABLE 2 *Presence of diabetes or obstruction of the urinary tract 42 cases of renal papillary necrosis*

Obstruction of Urinary Tract	Diabetes Mellitus			
	Present	Absent	Indeterminate	Total
Present	2	27	2	31
Absent	5	3	3	11
Total	7	30	5	42

Levaditi[13] produced papillary necrosis in rabbits by the injection of vinylamin, and Mandel and Popper[14] similarly produced the lesion in 36 rabbits and one dog Thus, renal papillary necrosis has been reproduced in the absence of both diabetes mellitus and obstruction or infection of the urinary tract

MATERIAL

Forty-two patients who had renal papillary necrosis came to necropsy at the Mayo Clinic from January 1934, through December 1954 The distribution of these patients according to age and sex is shown in table 1, and the presence of diabetes mellitus or obstruction of the urinary tract is indicated in table 2 Female diabetic patients with renal papillary necrosis outnumbered males with the same condition 4 to 3, whereas among those who did not have diabetes, males predominated 21 to 9 Presence or absence of diabetes was not ascertained in 5 cases There were 86 women among 120 diabetic patients and 54 men among 80 nondiabetic patients in reports of renal papillary necrosis in the literature, the sex was not stated in some cases The predominance of males with renal papillary necrosis but without diabetes undoubtedly is related to the frequency of urinary obstruction in older men

Surprisingly, the vast majority (81 per cent) of our patients did not have diabetes We cannot account for this disparity Actually, however, since the incidence of diabetes mellitus found at necropsy varies from 2 7 to 4 per cent, the incidence of 19 per cent for papillary necrosis among diabetic patients in our series indicates that the rate of occurrence of the renal disease is higher among diabetic persons than it is among the general population This prevalence probably is not so extreme as indicated by some other reporters

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[13] Levaditi C Experimentelle Untersuchungen uber die Nekrose der Nierenpapille Arch internat pharmacodyn 8 45 63 1901

CLINICAL MANIFESTATIONS

The clinical picture of renal papillary necrosis is extremely variable, but the disease may be divided roughly into subacute and acute types In the subacute form the development and progression of renal infection usually are slow, the increase in blood urea is progressive, oliguria comes about and death finally occurs Twelve of our patients had this form of the disease, five were diabetic When obstruction of the urinary tract and complicating cardiovascular disease are present, the clinical picture may in no way suggest the diagnosis of papillary necrosis, since the situation is characterized principally by the primary pathologic processes, and with terminal progressive oliguria and uremia uncomplicated by infection of the urinary tract Three of our patients had this condition

The acute type has two forms Fulminating renal infection may develop, with fever, septicemia, rapidly progressing azotemia and oliguria, a situation which finally terminates in coma and death On the other hand, if obstruction of the urinary tract is present, the picture may be essentially that of the obstructive disease until it is complicated by a terminal, acute, renal infection which rapidly progresses to uremia, oliguria and death Twenty-three of our patients had this acute type of disease, two were diabetic The remaining four patients died at home or in another institution, so that the terminal course is unknown to us

The disease usually is fatal, although cases in which spontaneous healing and recovery ensued have been reported [3, 6, 9, 14] In most of the latter cases the disease was unilateral only, to date no case in which recovery followed unequivocal bilateral involvement has been reported

Clinical findings most often made are pain in the flank, chills and fever, hematuria, dysuria, urgency and frequency of urination, nausea and vomiting, prostration and coma In all cases oliguria occurs, at least terminally, with associated mounting uremia and finally coma Death usually results from either uremia or overwhelming infection

DIAGNOSIS

The symptoms of papillary necrosis usually are masked by those of the primary disease, so that only a few antemortem or preoperative diagnoses have been reported [3, 6, 7, 9, 14, 15] In these the diagnosis was confirmed roentgenologically or by examination of tissue sequesters obtained in the urine The correct diagnosis rarely was suspected antemortem among our patients, and was confirmed in only one case (fig 1)

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[14] Wall, Bithel Pyelographic changes in necrotizing renal papillitis J Urol , 72 1-5, 1954

[15] Johnston, D H Repeated bouts of renal papillary necrosis diagnosed by examination of voided tissue Arch Int Med 90 711-717, 1952

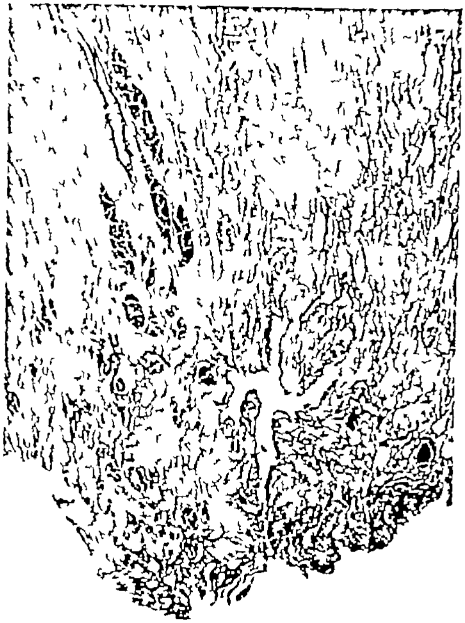

FIG 1 Portion of sequestered necrotic pyramid obtained at cystoscopy from diabetic patient, demonstrating typical ghostlike preservation of pyramidal architecture in necrotic papilla Note dark masses of organisms in tubules (hematoxylin and eosin, × 30)

The pyelographic picture[16] is similar to that of renal tuberculosis It results from erosion and destruction of the renal papillae (fig 2) All gradations of papillary necrosis may occur, hence, the roentgenologic appearance of the calyces depends upon the degree of necrosis Alternate areas of constriction and dilatation of the pelvis and calyces may be found, but the most pathognomonic findings are the irregular dilatation and "moth-eaten" appearance of the minor calyces which result from necrosis and sloughing of the renal papillae In advanced lesions there may seem to be extravasated contrast medium extending into the renal cortex parallel to the tubules, somewhat similar to pyelotubular backflow, from which it must be distinguished This finding was emphasized particularly by Gunther[7]

The diagnosis frequently has been established or confirmed only after unilateral nephrectomy[2 4 7 9] Gunther[2] reported three such cases, in which two patients survived

DIFFERENTIAL DIAGNOSIS

Diseases which must be distinguished from renal papillary necrosis are 1) acute pyelonephritis, without papillary necrosis, 2) calculus, with renal colic, 3) renal tuberculosis and 4) renal tumor Pyelonephritis without papillary necrosis is not so severe or so fulminating as when pyramidal disease is present, the patient is rarely so ill, and the response to conservative measures may rule out the more serious diagnosis Roentgenologic studies occasionally may distinguish

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[16] Braasch W F and Emmett J L Clinical Urography An Atlas and Textbook of Roentgenologic Diagnosis Philadelphia W B Saunders Co 1951 pp 690-691

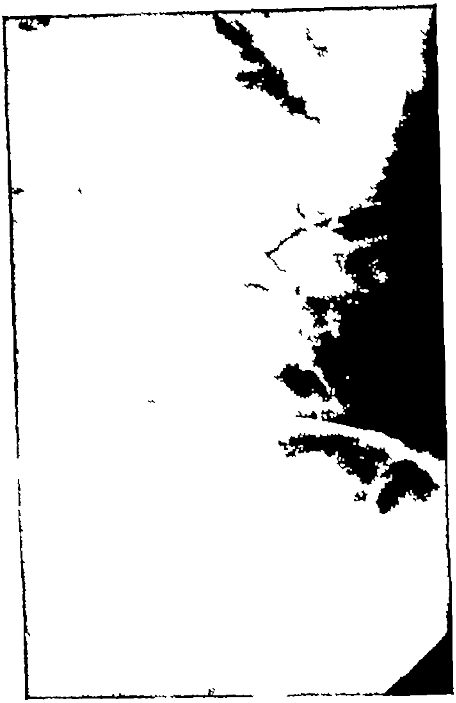
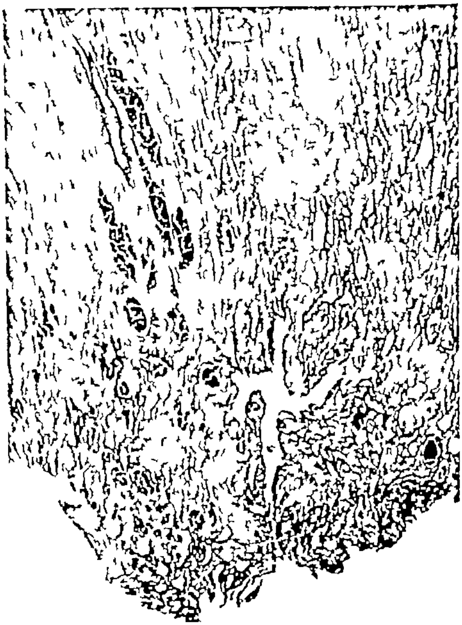


FIG 2 Left retrograde pyelogram Renal outline is enlarged with bizarre distortion and destruction of all calyces, suggestive of renal papillary necrosis Note extravasation of contrast medium parallel to tubules and extending toward renal cortex in some calyces particularly upper calyx

papillary necrosis, but not always The passage of a renal calculus in the presence of colic may be confused with the passage of a sloughed necrotic papilla The roentgenogram may be diagnostic in such cases, but frequently nonopaque calculi and sloughed tissue may resemble each other and make distinction impossible When hematuria is a presenting symptom both renal tuberculosis and tumor (of the renal pelvis) may produce a roentgenologic picture resembling that of papillary necrosis Differential diagnosis, particularly as between renal papillary necrosis and tuberculosis may be extremely difficult The fact that papillary necrosis usually is bilateral permits distinction from tumor in most cases The acuteness of the clinical picture also will incline the diagnosis toward papillary necrosis in distinguishing it from tumor or tuberculosis

PATHOLOGIC ASPECTS

Gross appearance Renal papillary necrosis was bilateral in 27 cases and unilateral in 12 cases (31 per cent) In the remaining three cases it occurred in patients who had a solitary kidney Unilateral involvement in 10 of our 12 cases could be explained on the basis of unilateral obstruction, with papillary necrosis found only on the involved side affected by obstruction In the other two instances predisposing factors (which will be discussed later) were present in both kidneys, but papillary necrosis developed only on the side with the most severe predisposing processes



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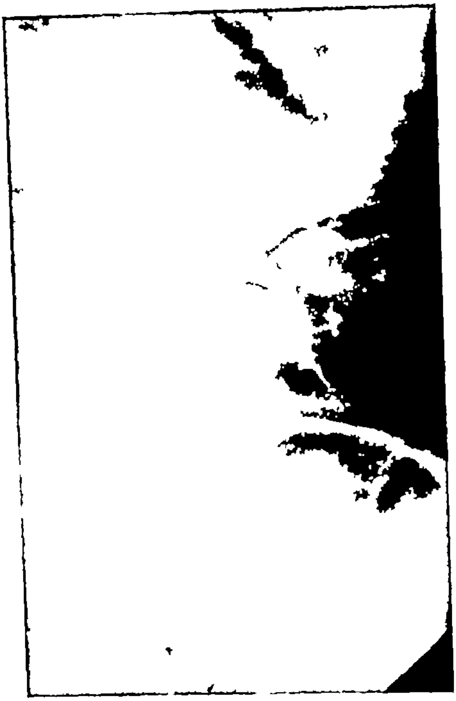
[16] Braasch, W F and Emmett J L Clinical Urography An Atlas and Textbook of Roentgenologic Diagnosis Philadelphia W B Saunders Co 1951 pp 690-691



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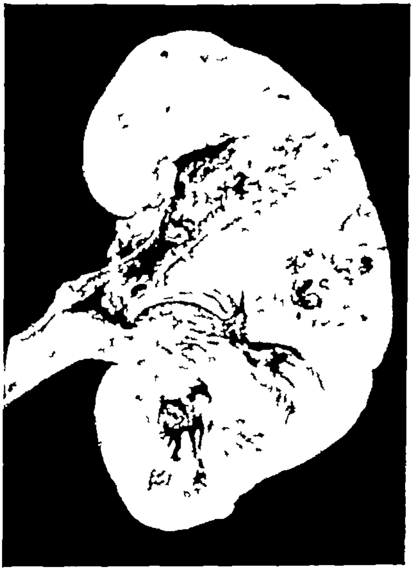

FIG 3 Gross specimen of kidney affected by typical lesions of renal papillary necrosis Note zone of demarcation between necrotic area of pyramid and adjacent viable parenchyma Patient did not have diabetes

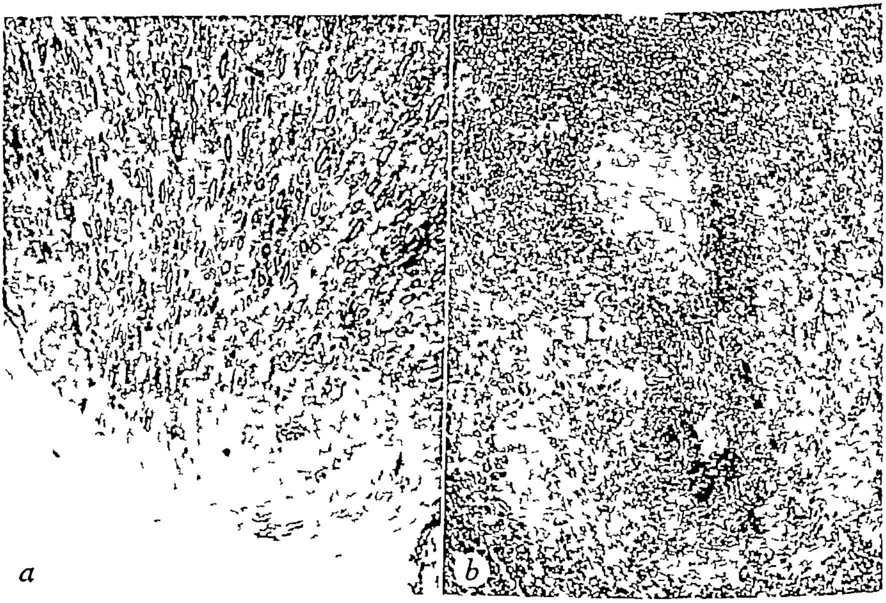

FIG 4 *a*, Necrosis involving only tip of renal pyramid Note zone of demarcation between involved and non necrotic areas (hematoxylin and eosin, × 23) *b*, Early lesion located proximally in pyramid Note heavy leukocytic infiltrate between necrotic and non necrotic tissue, and preservation of tubules with absence of cellular outlines ("ghostlike" preservation) in necrotic areas (hematoxylin and eosin, × 30)

The papillary portion of the medullary pyramids shows the characteristic lesion The degree of involvement varies with the severity of the process Multiple papillae are almost always affected The yellow-white, green or dark red necrotic papillae stand out in striking contrast to the remainder of the renal parenchyma

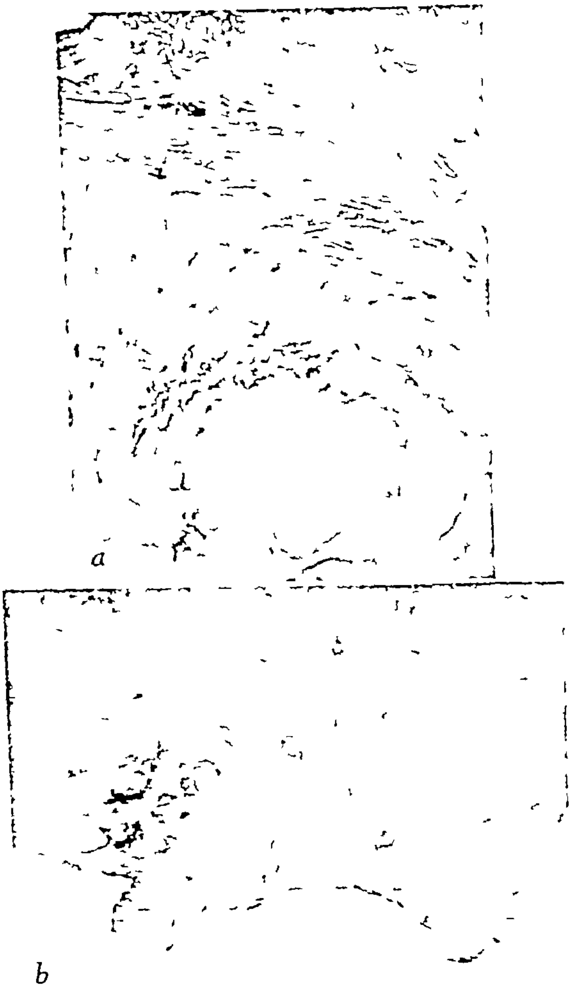

FIG 5 *a* Almost complete separation of necrotic papilla This stage would be represented as a 'ring shadow" roentgenologically (hematoxylin and eosin × 20) *b* Papilla has completely sloughed away leaving concave defect in pyramid base of which is well organized and healed This would be represented as clubbed calyx roentgenologically (hematoxylin and eosin × 75)

(fig 3) The tips of the papillae may be covered with a shaggy, grayish-white or hemorrhagic exudate The necrosis is coagulative characteristic of an infarct, and usually there is a sharp yellow-to-red zone of demarcation between the necrotic area and viable parenchyma Separation and sloughing of the necrotic papillae may occur along this line, with the fragment passing into the renal pelvis, leaving in its wake an irregular, gray, necrotic concavity extending into the pyramid Occasionally, only the tip of the papilla may be affected, or a small area of necrosis may be found only in the central portion of the pyramid, usually paralleling the long axis of the collecting tubules Sometimes the entire pyramid may be necrotic The columns of Bertin and the renal cortex generally are uninvolved in the necrotic process

Microscopic appearance The renal cortex, pelvis and calyces reveal the usual changes of acute or chronic pyelonephritis, hydronephrosis or other associated pathologic conditions

Dilatation of the tubules frequently was noted, particularly when obstruction was present, with degenerated leukocytes and amorphous debris in the lumens Degenerative changes were noted in the epithelial cells of the tubules in all cases, ranging from simple, cloudy, granular cytoplasm to necrosis The interstitial tissue was most often characterized by edema, inflammatory-cell infiltration, fibroblastic proliferation and formation of abscesses

The typical lesion of papillary necrosis is found in the papillary portion of the renal pyramids, and consists of an infarct with coagulation necrosis of all the elements and early, good preservation of the general underlying architecture (so-called ghost papillae) Abscesses were observed in the renal pyramids in 38 cases When acute pyelonephritis was not present, development of such abscesses undoubtedly was the result of secondary infection of the necrotic areas and subsequently the adjacent parenchyma

Edema of some degree and necrosis were observed in all cases except one In many necrotic areas with loss of cellular detail, the general architecture persisted, with pyknosis or absence of cell nuclei Later, all the tissue became necrotic, losing its architectural pattern The necrotic areas were most often found in the distal portion of the pyramid, although a more proximal location frequently was found (fig 4) When the necrotic tissue sloughs, the remaining

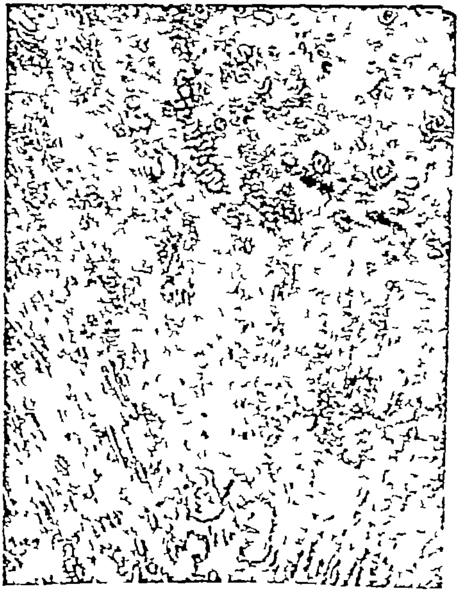

FIG 6 Juxtamedullary area of kidney in case of chronic pyelonephritis demonstrating thickening of arterial wall at edge of adjacent area of necrosis in pyramid Note lack of inflammatory exudate in zone of demarcation Necrosis resulted from ischemia caused by arteriosclerosis (hematoxylin and eosin × 19)

TABLE 3 *Combinations of factors of etiologic importance 42 cases of papillary necrosis in which necropsy was done*

		Cases No
A	Acute pyelonephritis + Vascular (chronic pyelonephritis arteriosclerosis) + Diabetes	3
B	Acute pyelonephritis + Vascular (chronic pyelonephritis arteriosclerosis) + Diabetes + Obstruction	2
C	Acute pyelonephritis + Vascular (chronic pyelonephritis) + Diabetes	1
D	Acute pyelonephritis + Vascular (chronic pyelonephritis, subacute bacterial endocarditis) + Diabetes	1
E	Acute pyelonephritis + Vascular (chronic pyelonephritis) + Obstruction	17
F	Acute pyelonephritis + Vascular (chronic pyelonephritis arteriosclerosis) + Obstruction	5
G	Acute pyelonephritis + Vascular (chronic pyelonephritis, lupus erythematosus)	2
H	Acute pyelonephritis + Vascular (chronic pyelonephritis periarteritis nodosa)	1
I	Acute pyelonephritis + Obstruction	4
J	Acute pyelonephritis	1
K	Vascular (chronic pyelonephritis arteriosclerosis) + Obstruction	1
L	Vascular (chronic pyelonephritis congestion*) + Obstruction	1
M	Vascular (congestion†) + Obstruction	1
N	Vascular (chronic pyelonephritis congestion‡)	1
O	Vascular (erythroblastosis fetalis)	1
	Total	42

* Congestion resulted from shock with peripheral vascular collapse
† Congestion resulted from cardiac failure after myocardial infarction
‡ Congestion resulted from renal vein thrombosis

margin of the pyramid is irregularly concave, and consists of varying amounts of necrotic material and the reactive zone, as described (fig 5) Healing was observed in two cases and was complete in one

Impairment of circulation was evident in all but five of our cases Sclerosis of the arterial tree accompanying chronic pyelonephritis was seen in 35 cases (fig 6) This varied from slight-to-marked medial thickening and adventitial fibrosis, and gave the characteristic "onion-skin" appearance In some cases when the disease was severe, this was associated with intimal thickening Moderate-to-severe arteriosclerosis was noted in 11 cases

In three cases severe vascular congestion with stasis and local tissue anoxia accompanied the infarction The causes of this congestion were renal-vein thrombosis, cardiac failure, and shock with peripheral vascular collapse, each occurring in a single case

COMMENT ON CAUSATION

The various combinations of factors contributing to the causation of papillary necrosis in the 42 cases reported are outlined in table 3 The multiplicity of contributing conditions is evident By far the *commonest combination of factors* serving to deplete the pyramidal blood supply and to result in papillary necrosis was acute pyelonephritis accompanied by vascular changes, as occurred in 32 cases

Obstruction of the urinary tract, with dilatation of the renal pelvis and calyces, and resultant dilatation of the collecting tubules in the renal pyramid, can serve further to embarrass circulation in this area by compression of the interstitial tissues and the small blood vessels contained therein (24 cases) Interstitial edema may cause compression of the small vessels in the pyramids Formation of abscesses, with involvement of the adjacent vessels, similarly may result in vascular occlusion

The potentiation of acute pyelonephritis by either diabetes or obstruction of the urinary tract is well established

TREATMENT

The almost uniform fatality resulting from bilateral papillary necrosis emphasizes the necessity of prevention, rather than treatment, of this disease Early recognition and prompt adequate treatment of acute pyelonephritis, in both the diabetic and the nondiabetic patient, are essential Similarly, early recognition and relief of obstructive urologic disease is vital Good diabetic control probably will help to prevent this disease among patients so afflicted, although the duration and severity of the diabetes are not generally considered to be of importance etiologically [4] The frequently insidious symptoms of obstructive urologic disease and of renal infection, particularly in diabetic patients, may continue to be sources of delay and frustration

To date, spontaneous recovery from proved bilateral papillary necrosis has not been reported Those patients who recovered spontaneously or recovered after nephrectomy probably had unilateral involvement only In such cases control of infection and relief of urinary obstruction are vital In addition, the advisability of nephrectomy must be considered Cases in which unilateral nephrectomy was followed by clinical recovery have been reported [3, 4, 9] In none of these was contralateral papillary necrosis demonstrated Whether or not nephrectomy was lifesaving in these cases is purely conjectural Certainly, nephrectomy is contraindicated if the integrity of the contralateral kidney is in question

SUMMARY AND CONCLUSIONS

The clinical and diagnostic features of renal papillary necrosis have been discussed

The present study of 42 cases brings the total reported to 253 In the majority (61 per cent) of those reported previously, diabetes mellitus was associated, whereas diabetes mellitus was associated in only 19 per cent of this series

It is apparent that no single factor can be cited as all-important in the pathogenesis of renal papillary necrosis The anatomically inferior blood supply of the pyramids serves to localize the necrotic process to its characteristic site in all cases Vascular changes were, or acute pyelonephritis was, evident in all instances, and both were present in more than three-fourths of the cases Obstructive urologic disease and diabetes mellitus, both serving to potentiate renal infection as well as further to compromise the pyramidal blood supply by virtue of their own inherent pathologic derangements, were encountered frequently as complicating factors

Treatment of renal papillary necrosis, in view of the almost invariable fatal termination, is largely supportive Control of infection and diabetes and relief of obstruction of the urinary tract are imperative

The frequent occurrence of renal papillary necrosis in nondiabetic persons, contrary to the incidence reported in the literature, is particularly emphasized

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EXPERIMENTAL EXTERNAL ESTIMATION OF RENAL BLOOD FLOW WITH RADIOACTIVE IODINATED ALBUMIN

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The estimation of renal blood flow is often of prime importance to the urologist endeavoring to decide preoperatively, in the face of total obstruction of indeterminate duration, whether the involved kidney is worthy of being spared, or whether immediate nephrectomy should be carried out. There may be no visualization on excretory urography, catheterization may be technically impossible mitigating against the use of divided clearances, and the visualization of the vascular pattern by aortography may be incomplete, or subject to errors of interpretation. The utilization of radioactive isotopes for the determination of peripheral blood flow,[1] cardiac output,[2] and the distribution of hepatic blood supply,[3] suggested to us that possibly the principles of external counting might be applied to the kidney.

TECHNIQUE AND RESULTS

To explore this concept, two sets of experiments were carried out utilizing healthy nembutalized mongrel dogs. In the first group of 7 animals, both kidneys were exposed through flank incisions. Ten to 15 microcuries of iodinated albumin (I^{131}) were then injected intravenously. By means of two scintillation counters in direct contact with the kidneys isolated by lead shields, the radiation from both was counted and recorded directly on a dual channel recorder. Then, with the blood supply to one kidney clamped, the same experiment was repeated using 25-30 additional microcuries as the repeat dose. Results showed that the counts obtained from the impaired side were definitely of a markedly lower order than those obtained from the contralateral side (fig. 1). The initial curves resembled those seen in the studies of peripheral vascular beds and occasionally were similar to the curves of cardiac output studies.

Similar experiments were then carried out in a series of animals with the kidneys in situ, and with a single scintillation counter applied externally counting through the intact flank. After preliminary counting on one side, the experiment was repeated with the kidney ligated. Both observations were then made on the

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This work was carried out with facilities made available through contract number W 31-109-ENG-78 between the United States Atomic Energy Commission and Western Reserve University.

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contralateral side The readings were then adjusted for background and for variation in dose so that representation is analogous in both sets of animals Ligation was carried out on both sides in the second group to prove that we were actually counting the radiation from the kidney The results in this group were also constant and paralleled very closely the marked disparity seen in the first group after clamping the renal vessels (fig 2)

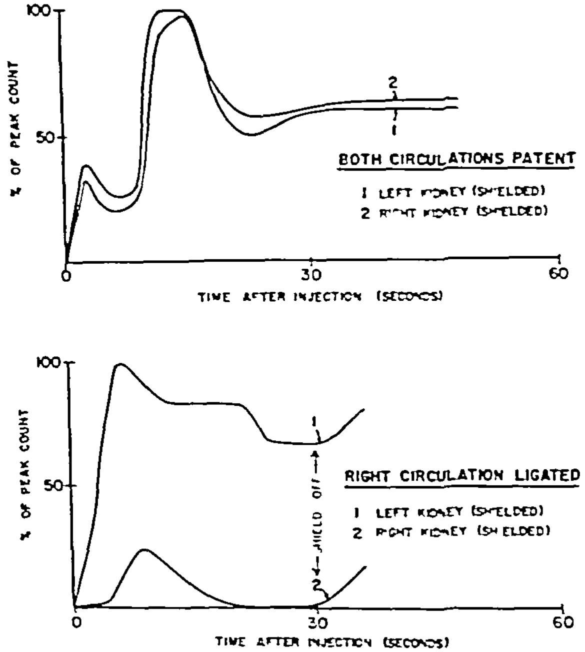

Fig 1 Counts obtained over exposed kidney of dog using iodinated albumin I^{131} intravenously (top) and change in counts obtained following unilateral ligation of renal vessels (bottom)

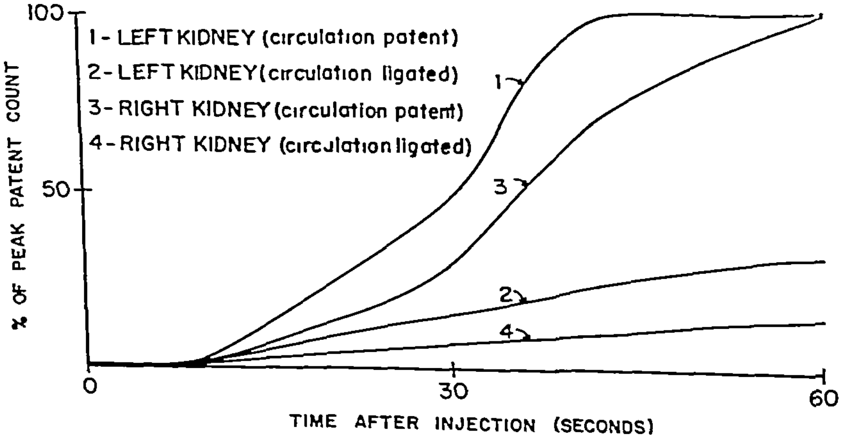

Fig 2 Counts obtained through intact dog's flank with blood supply to both kidneys open and then closed

DISCUSSION

The value of a simple method which would permit the urologist to determine preoperatively the state of the renal blood supply seems obvious We hope ultimately to apply these experiments clinically and to achieve a quantitative measure of the renal circulation It was feared that in the intact animal the counts from the viscera, soft tissues, and great vessels would be of sufficient magnitude to mask the lowering of counts on the side of embarrassed renal circulation The fact that this did not occur corroborates the recent observations of Winter[4] who utilized the external counting of radioactive diodrast as a test of renal function, and suggested possible extension of his technique to the determination of renal blood flow We feel that by the comparison of the counts obtained externally from both kidneys and utilizing in addition the counts obtained elsewhere away from the kidneys to represent a vascular bed akin to that through which the kidney counts are obtained, our study will give a quantitative measure of the renal blood flow similar to his determinations

SUMMARY

The feasibility of using external counting of radioactivity to evaluate renal blood flow has been demonstrated in the dog Extension of these studies to patients and a more exact determination of the quantitative aspects of these measurements are to be attempted

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A STUDY OF THE RENAL EXCRETION OF 3-AMINOPHTHALHYDRAZIDE

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The compound 3-aminophthalhydrazide was found by Albrecht in 1928 to have the property of producing chemiluminescence when treated with an oxidizing agent such as hydrogen peroxide, potassium ferricyanide or sodium hypochlorite in an alkaline solution. Several other phthalhydrazide derivatives produce chemiluminescence on oxidation but not nearly as much light as with 3-aminophthalhydrazide.

The production of light presented the intriguing thought that perhaps this compound would be excreted in the urine and if the amount of excretion varied with renal function this might be an easily performed renal function test.

In order to evaluate the physiological properties of 3-aminophthalhydrazide it was administered to a rabbit. It was found that it was impossible to dissolve 3-aminophthalhydrazide in any aqueous medium except in alkaline solution. Therefore 50 gm. 3-aminophthalhydrazide was dissolved in 1000 cc. of a 4 per cent sodium hydroxide solution and the pH adjusted to 8. This was then administered by means of a slow intravenous drip to a 4 pound rabbit to a total quantity of 0.5 gm./kilo. The urine was collected and was found to possess the typical luminescent properties of 3-aminophthalhydrazide. The rabbit appeared to suffer no untoward effects and was later sacrificed and no organic changes of the various organs found.

Another rabbit was given a subcutaneous injection of 1 gm. 3-aminophthalhydrazide suspended in peanut oil. This rabbit showed no untoward reactions and was kept for 6 years. Autopsy at that time revealed only fibrosis and a foreign body reaction about the previous site of injection.

In order to be absolutely sure no toxic effects would result from administration of this compound to human beings it was evaluated by the Toxicology Section of the U. S. Public Health Service Communicable Disease Center at Savannah, Georgia. They found, as aforementioned, that 3-aminophthalhydrazide was soluble only in a basic solution. The weakest base in which they found solution could be affected was a 5 per cent solution of sodium carbonate. Rabbits were selected for acute toxicity studies. 3-aminophthalhydrazide was administered intravenously as a 10 per cent solution in 5 per cent sodium carbonate. However, even with this weak base the animals were killed by alkalosis before the desired amount of compound to be tested could be administered. Therefore, no tests using this route of administration could be completed.

'The compound to be tested was given to rats by intraperitoneal injection in dosages of 500, 1000, and 2000 mg./kg., administered as a 20 per cent suspension in 5 per cent sodium carbonate. There were no noticeable differences between the rats receiving the control 5 per cent sodium carbonate solution and the rats

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receiving the material to be tested suspended in the same solution Most of the animals showed signs of alkalosis and peritoneal irritation

"Female white rats weighing around 200 grams were selected for the study of acute oral toxicity The compound was administered in gelatin capsules One group of three rats was given 500 mg /kg of the drug A second group of three animals received 1000 mg /kg Two additional groups were set up at levels of 1,500 and 2,000 mg /kg Due to difficulty with the dosing technique and the limited quantity of the drug available, only one animal was treated at each of the two higher levels A control group was set up in which the animals were given gelatin capsules containing pyrophyllite, a water-insoluble silicate, in the same manner as above None of the treated animals died, and during observation for 19 days following treatment, none showed symptoms of poisoning All of these animals continued to gain weight at the expected rate Thus it appears that up to 2,000 mg /kg of 3-aminophthalhydrazide may be given to rats as an acute oral or intraperitoneal dose with no ill effects The determination of the LD50 for this drug has not been carried out, for it is mechanically impossible to administer doses much larger than 2,000 mg /kg to rats

"Two rats were given the powdered drug, ground into their regular diet at levels of 5 and 10 per cent The food intake and body weight of these animals were checked daily The rat on the 5 per cent mixture consumed a total of 301 gm of the diet over the 19 days of observation, representing an average daily food intake of 15 9 gm The food intake was consistent, showing extreme daily values of 11 and 24 gm This is only slightly below average for a rat of this weight A slight gain in body weight was shown during the experimental period The total intake of the drug was 15 gm (85,000 mg /kg) during the 19 days of the test

"The animal which was fed on a 10 per cent mixture consumed a total of 206 gm of the diet, or an average of 10 1 gm per day This is considerably below the normal food intake, and the rat dropped in body weight from 177 to 174 gm during the course of the test This probably represents a dislike of the diet rather than toxicity of the drug The total drug consumption by this animal was 20 6 gm (116,384 mg /kg) "

Therefore, the conclusion reached by the Communicable Disease Center was that 3-aminophthalhydrazide possesses a very low order of toxicity for rats when given orally on an acute or a subacute basis

It was felt also that the oral route of administration would be the one to be used on patients as the intravenous or intramuscular route would be too toxic from pH standpoint

After completion of the toxicity studies it was necessary to devise a method of quantitatively measuring the amount of 3-aminophthalhydrazide in a given solution

It was thought that the amount of luminescence could be used as a quantitative measure of the amount of 3-aminophthalhydrazide present

The amount and duration of light produced, however, vary with several factors besides the concentration of 3-aminophthalhydrazide

1) The alkalinity of the solution causes variations in the amount of lumines

cence produced The maximum luminescence occurs with a solution of 0 015 normal sodium hydroxide as found by Zellner and Dougherty As the concentration of sodium hydroxide is increased the amount of light produced drops off until in a 0 5 normal sodium hydroxide solution only 1/8th as much light is produced The reaction does not occur at all in acid solutions

2) The concentration of 3-aminophthalhydrazide affects the amount of light produced in the oxidation but it is not a direct proportion It has been found by Leedy that the maximum light is produced when the concentration of 3-aminophthalhydrazide is 0 02 molar A 0 5 molar solution causes only half the amount of light as the 0 02 molar solution Luminescence will occur, however, with 3-aminophthalhydrazide in as extremely a great solution as one part of 3-aminophthalhydrazide to 10^8 parts of water

3) Luminescence will occur with only hydrogen peroxide as the oxidizing agent but although the duration is long the amount of light produced is low The intensity is increased markedly with such compounds as potassium ferricyanide or sodium hypochlorite, manganese dioxide, colloidal platinum, hemoglobin and ozone It is felt by some authors that these act as catalysts to the oxidation We have found that a satisfactory reaction occurs with only potassium ferricyanide as an oxidizing agent Thus it can be seen that several variables enter into the amount of luminescence produced on oxidation of 3-aminophthalhydrazide

It was thought that perhaps the amount of 3-aminophthalhydrazide present in a solution could be determined by titrating the solution with an oxidizing agent such as potassium ferricyanide until all the 3-aminophthalhydrazide has been oxidized, the end point being the failure of a drop of potassium ferricyanide to produce any luminescence on striking the surface of the solution of 3-aminophthalhydrazide In order to do this it was found necessary to add an excess of sodium hydroxide to the solution of 3-aminophthalhydrazide (The 3-aminophthalhydrazide solution was prepared by dissolving 0 5 gm of 3-aminophthalhydrazide in 1 liter of 0 5 per cent sodium hydroxide To some quantities of this was added equal parts of 5 per cent sodium hydroxide) The titration was carried out in the dark using 0 1 per cent solution of potassium ferricyanide for titration However, not only was it quite difficult to titrate in total darkness but also the end point was inadequate

Another and better way was found to quantitatively measure the amount of 3-aminophthalhydrazide present in a certain solution and that was by fluorescence There is no chemical reaction involved and, therefore, the number of variables is decreased to three, that of the amount of 3-aminophthalhydrazide, the amount of ultraviolet light used, are the pH of the solution In contradistinction to the luminescent reaction, fluorescence occurs only in a neutral or acid solution Weber found that the fluorescence occurred in a solution with a pH of from 2–8 The maximum fluorescence occurred at a pH of 4 86

Our experiment showed that the greatest fluorescence occurred in a neutral solution A Coleman universal spectrophotometer with a photofluorometer attachment was used for the determinations A UV 1 filter passing only the 365 M U band was placed between the ultraviolet illumination and the solution A PC 1 filter was placed in front of the photoelectric cell to filter out all light except the purplish-blue light from the fluorescing 3-aminophthalhydrazide solution

The neutralized solutions of 3-aminophthalhydrazide were placed in quartz cuvettes under the ultraviolet lamp and the amount of fluorescence measured with the aid of the Wheatstone bridge and string galvanometer of the spectrophotometer It was found that if the solution of 3-aminophthalhydrazide was too concentrated the surface of the solution fluoresced more brilliantly than the remainder and, therefore, the total light output of the solution was less Therefore, it is necessary to be sure that the solution is dilute enough so that the fluorescence is even throughout It was found that a 5 mg per cent solution of neutralized 3-aminophthalhydrazide fluoresced more at the top and therefore gave a lower reading than a 2 5 mg per cent solution Therefore, a 2 5 mg per cent solution was used as the standard for all determinations This standard was prepared as follows First a 50 mg per cent alkaline stock solution of 3-aminophthalhydrazide is made by dissolving 100 mg of 3-aminophthalhydrazide in 200 cc of 0 01 normal sodium hydroxide The standard is then made from this by taking 5 cc of the stock solution and adding 5 cc of 0 01 normal sulfuric acid and diluting to 100 cc thus forming a neutral standard solution It has been found that the alkaline stock solution is quite stable and will keep for many months However, the neutralized standard drops in the amount of fluorescence it will produce after a few days

By appropriate dilutions of the standard the calibration curve shown in figure 1 was obtained It was found that this method of measurement was quite accurate and the results were reproducible when an aqueous solution was used

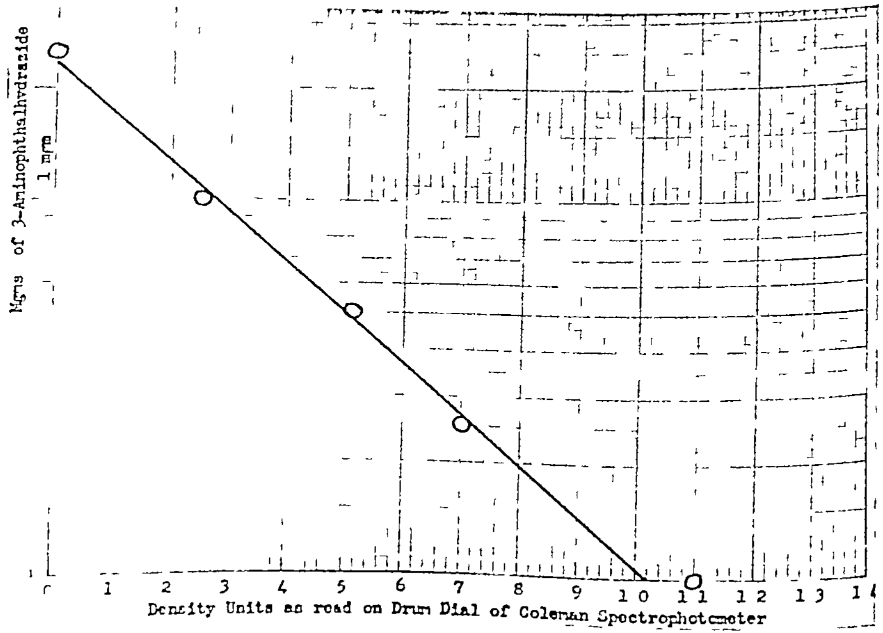

FIG 1 Calibration curve for use with 2 5 mg per cent standard of 3 aminophthalhydrazide

The next phase of the investigation involved giving patients 3-aminophthalhydrazide by mouth, collecting the urine and determining the amount excreted. Normal urine was first placed in the spectrophotometer. This was found to fluoresce very slightly with a reading of 1.5 density units (as compared to the standard set to 0 density units on the drum dial of the spectrophotometer). A normal young male was given 0.5 gm. of 3-aminophthalhydrazide at 6:00 a.m. and all urine saved for the next 6 hours. On placing a specimen of this urine in the spectrophotometer it fluoresced brightly but all at the surface. It was found necessary to dilute the urine 1:10 with water to obtain fluorescence even enough for satisfactory readings. It seems that concentrated urine blocks the ultraviolet light from penetrating deeply into the solution.

Next the total duration of the output of 3-aminophthalhydrazide in a normal individual was determined. It was found that after collecting urine in hourly specimens for ten hours that very little 3-aminophthalhydrazide was excreted in the first hour. During the second hour more was excreted. During the next eight hours equal amounts were excreted. It was evident that the excretion extended beyond ten hours. Therefore, two other normal male patients were given 0.5 gm. of 3-aminophthalhydrazide and all urine collected in six hourly specimens for 30 hours. The results are seen in table 1.

It is, therefore, seen that the majority of the 3-aminophthalhydrazide was excreted in the first 6 hours. In the first patient 64 per cent and 74 per cent in the second was excreted in the first 6 hours. However, it was excreted for 24 hours in measurable amounts. It was found in other cases that it was excreted for over thirty-six hours.

To evaluate the excretion of 3-aminophthalhydrazide in a patient with decreased renal function a forty-year-old man with polycystic disease was chosen. The nonprotein nitrogen was 100 mg. per cent. An excretory urogram showed no dye in 30 minutes. However, he was asymptomatic. Three normal individuals were chosen as controls. Each patient was given 0.5 gm. of 3-aminophthalhydrazide. Table 2 shows the results.

It is noted that three to four times as much 3-aminophthalhydrazide was excreted by the patient with the elevated nonprotein nitrogen due to polycystic

TABLE 1

Time of Specimen	Volume	Mg. % of 3 amino-phthalhydrazide in urine	Total mg. for each 6 hours	Total mg. output
6 a.m.–noon	400 cc	7.2	28.8	39.3
Noon–6 p.m.	1100 cc	.6	6.6	
6 p.m.–Mid.	650 cc	.6	3.9	
Mid.–6 a.m.	950 cc	None	None	
6 a.m.–Noon	450 cc	None	None	
6 a.m.–Noon	500	4.4	22.0	27.7
Noon–6 p.m.	300	1.6	4.8	
6 p.m.–Mid.	180	.3	0.6	
Mid.–6 a.m.	80	.3	0.3	
6 a.m.–Noon	650	None	None	

TABLE 2

	Time of specimen	Volume	Mg % of 3 amino phthalhydrazide in urine	Total mg for each 6 hours	Total mg output
		cc			
Patient with polycystic disease	6 a m -noon	900	6 5	58 5	400 9
	noon-6 p m	820	8 7	71 4	
	6 p m -mid	1300	8 0	104	
	mid -6 a m	780	7 0	55	
	6 a m -noon	900	7 8	79	
	noon-6 p m	600	7 0	42	
Normal	6 a m -noon	120	10 0	12	126 8
	noon-6 p m	210	9 6	20	
	6 p m -mid	180	9 6	17 3	
	mid -6 a m	500	6 5	32 5	
	6 a m -noon	300	7 5	22 5	
	noon-6 p m	300	7 5	22 5	
Normal	6 a m -noon	600	7 0	42	167 4
	noon-6 p m	760	5 4	41	
	6 p m -mid	570	5 4	31	
	mid -6 a m	540	3 9	21	
	6 a m -noon	600	2 8	16 8	
	noon-6 p m	600	2 6	15 6	
Normal	6 a m -noon	690	6 5	45	98 5
	noon-6 p m	500	5 4	27	
	6 p m -mid	250	5 0	12 5	
	mid -6 a m	240	2 5	6 0	
	6 a m -noon	510	1 6	8 0	
	noon-6 p m	300	Insignificant	—	

disease Dr Peterson found a similar thing to be true in the qualitative evaluation of the excretion of 3-aminophthalhydrazide by several patients with impaired renal function The full meaning of this is not clear to the investigators at the present time Further work will be necessary to explain this and to properly evaluate this as a type of renal function study It is also realized that in the average individual only one-third to one-fifth of the 3-aminophthalhydrazide ingested is excreted in the urine Whether or not this is due to lack of absorbtion from the intestinal tract, or if it is all absorbed whether or not the liver excretes the remainder is not known It is also possible that this compound, being such a readily oxidizable substance, is oxidized by the bloodstream into a form that is not luminescent or fluorescent As was mentioned before, hemoglobin acts as a catalyst to the oxidation

All these questions and many more will have to be answered before the pharmacology of 3-aminophthalhydrazide will be completely understood It is felt by the authors that at this time enough material concerning the excretion of this compound by the kidneys has been accumulated to warrant reporting on the subject

SUMMARY

The compound 3 aminophthalhydrazide is known to have the property of both chemiluminescence on oxidation and fluorescence under ultraviolet light The thought that this compound might be excreted in the urine and if so could be measured quantitatively presented itself The compound was therefore given to animals and prompt urinary excretion obtained Toxicity was found to be very low when the compound was given orally Due to the necessity of its being dissolved in an alkaline solution parenteral administration was not possible

A quantitative method of measuring the concentration of 3-aminophthalhydrazide in a given solution was next developed The property of chemiluminescence was found to be variable for quantitative measurement so fluorescence in a Coleman spectrophotometer was used Patients were then given 3-aminophthalhydrazide orally It was found that the urinary excretion extended over a period of 36 hours in most cases It was also found that a patient with an elevated non-protein nitrogen elimination due to polycystic disease put out three to four times as much 3-aminophthalhydrazide as did normal patients The full significance of this is not known and further study is indicated

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RENAL AND OSSEOUS MANIFESTATION OF TUBEROUS SCLEROSIS
CASE REPORT

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Tuberous sclerosis has been recognized as a disease entity since 1880,[1] and the classical triad of epilepsy, mental retardation, and adenoma sebaceum which characterizes the disorder has been appreciated since 1908[1] While tuberous sclerosis is often referred to as one of the neurocutaneous syndromes[2-4] other tissues are frequently involved It has been stated that over 80 per cent of all cases have multiple kidney tumors and cysts,[5, 6] but these have rarely been diagnosed during life Pulmonary cystic disease and cysts and myomas of the heart, lungs, liver and pancreas[6, 7, 8] are also occasionally seen The bones are frequently involved in the process and radiographically the lesions have variously consisted of patches of dense bone in the skull,[2, 4, 8, 9, 10] osteoporosis, cystic changes and periosteal thickening,[1, 4, 10] especially of the bones of the hand Calcifications of the lesions of the lateral ventricles and the "candle gutterings" seen on air encephalography typify the disease[3, 4] The case at hand presents the typical clinical and radiographic findings of the disease and in addition demonstrates osseous and renal abnormalities radiographically

CASE REPORT

A 40-year-old white woman was admitted to the Deaconess Hospital on May 2, 1955 with complaints of right renal colic, hematuria, burning and frequency of urination Her symptoms were of 1 week's duration

Her past history revealed that as a child she had had convulsive seizures which began at the age of 18 months, and ceased after age 14 years Also at the age of 14 years she began having migratory joint pains associated with a blowing systolic apical heart murmur, and a diagnosis of rheumatic heart disease was made She stated that the skin lesions over the bridge of the nose and cheeks had

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Read at annual meeting, North Central Section of American Urological Association, Cleveland, Ohio, October 3-5, 1956

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FIG 1 Portion of elevated nodule showing imperfect hair follicles and sebaceous gland and fibrous tissue proliferation Microscopic picture is that of adenoma sebaceum

been present as long as she could remember and had been diagnosed as hypertrophic acne papillomas and on one occasion by a dermatologist, as adenoma sebaceum after a biopsy (fig 1) Since 1945 she had had numerous attacks similar to the current one and was usually found to have blood and pus in the urine

There was no family history of mental retardation carcinoma heart disease or kidney disease The patient had three full term pregnancies all of which were terminated by caesarean section The first baby died shortly after birth the second at the age of 1 year with convulsive seizures the cause of which were undetermined and the third at the age of 6 years following appendectomy In 1940 she had a pilonidal cyst removed, in 1945 a hysterectomy and in 1947 a cholecystectomy for cholelithiasis

Physical examination disclosed a well developed, well nourished white woman of low mentality She had numerous nodular rubbery skin lesions in a butterfly distribution over the nose and cheeks (fig 2) The patient also had an area of hypertrophic skin in the occiput and two areas in the low back region which were painful to palpation The right kidney mass was palpable while the left was not Her blood pressure ranged from 130 84 to 172 140 The remainder of the physical examination was entirely negative

Laboratory findings Kahn negative RBC 4 460 000 WBC 7 750 Hemoglobin 13 5 gm Polymorphonuclears 65 per cent Lymphocytes 31 per cent Monocytes 3 per cent Eosin 1 per cent Serum calcium 10 mg per cent Serum phosphorus 3 5 mg per cent Alkaline phosphatase 8 units Acid phosphatase 5 units Urinalysis was normal

X-ray findings Survey films of the abdomen demonstrated the kidney masses to be large in size indistinct in outline and to have a peculiar reticulated pattern of density This reticulated pattern consisted of areas of radiolucence with a fibrotic periphery Retrograde and intravenous pyelograms showed elongated major calyces and renal pelves with multiple rounded impressions on the collecting structures (fig 3) Discrete areas of dense bone were noted in the

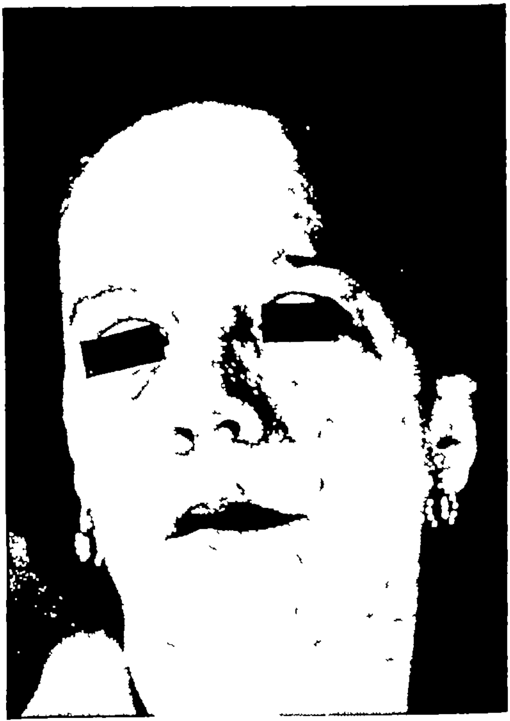

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FIG 2 Butterfly distribution of hard rubbery nodules which pathologically proved to be adenoma sebaceum

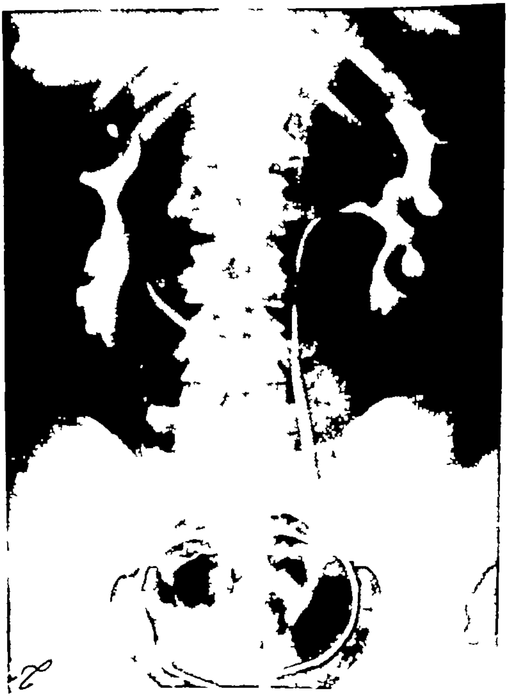

FIG 3 Elongated renal pelves with multiple rounded impressions on the collecting structures Course of right ureter is at least suggestive of retrocaval ureter It is impossible to reproduce radiolucent areas of kidney parenchyma described in text

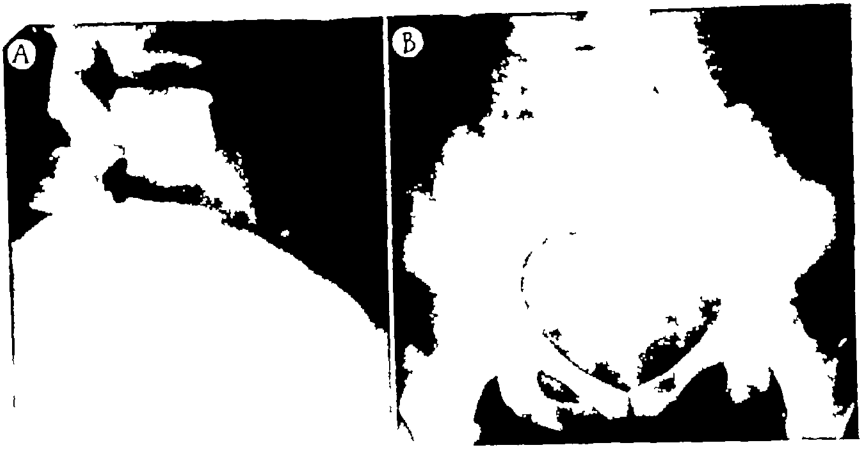

FIG 4 Discrete areas of dense bone are present in wings of ilia bodies of lumbar vertebrae, as well as spines and transverse processes of lumbar vertebrae These are similar radiographically to bone lesions found usually in skull

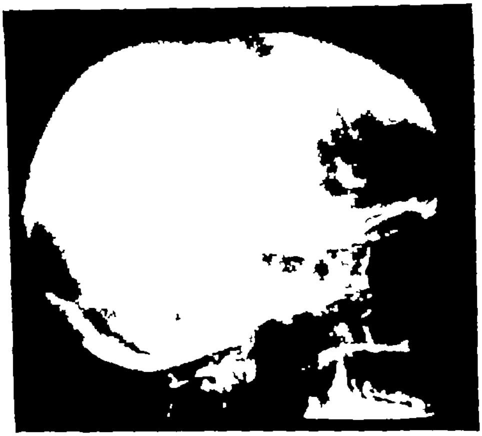

FIG 5 Well circumscribed areas of density, most of which were stereoscopically within skull bones themselves Pineal gland is also calcified

wings of the ilia, the bodies, spines, and transverse processes of the lumbar vertebrae (fig 4) Skull films revealed several areas of calcification most of which stereoscopically appeared to be within the skull bones themselves (fig 5) The ribs and long bones were normal, and the chest radiograph was not remarkable

The patient was treated with gantrisin and supportive measures The urinary symptoms promptly subsided and the patient was discharged from the hospital after 1 week

DISCUSSION

The radiographic findings of the presented case were extensive and supported the clinically evident diagnosis of tuberous sclerosis

The discrete areas of dense bone in the skull have been previously described, although the literature fails to reveal descriptions of the similar bone lesions found in the lumbosacral spine and pelvis Likewise intracranial calcifications are frequently present in cases of tuberous sclerosis, although even in their absence, the nodules found adjacent to the lining of the ventricles may be demonstrated by an encephalography

Bourneville's original case in 1880 had bilateral kidney tumors demonstrated at autopsy The radiographic appearance of the kidneys is similar to polycystic kidneys Indeed, pathologically, some of the tumors of the kidneys prove to be cystic, but most of the tumors are lipomas, hamartomas, myomas, or angiomas The reticulated pattern noted in the kidney parenchyma may be due to the presence of a lipomatous component within the tumor and may be an aid in differentiating these tumors from polycystic kidneys Some authors have considered the tumors to be variants of Wilms tumors or hypernephromas The incidence of malignant degeneration is considerable[11]

Benign and malignant tumors, especially rhabdomyomas, are sometimes found in the liver and heart Cystic disease of the lung and pancreas are also occasionally found The protean nature of the disease is well illustrated by the presented case

SUMMARY AND CONCLUSIONS

The literature is briefly reviewed

A case presenting the typical clinical picture of tuberous sclerosis and exhibiting interesting radiographic findings in bones and kidneys is discussed

It is believed that any patient with pyelograms consistent with the diagnosis of polycystic kidneys should be evaluated neurologically, and conversely, if abnormal skull densities or intracranial calcifications are identified, the kidneys should be investigated by pyelography

A radiographic sign which may be useful in the differential diagnosis of renal hamartomas and polycystic kidney disease is presented

The inclusion of tuberous sclerosis as one of the so-called neurocutaneous syndromes is probably unjustified, due to the frequency of involvement of tissues of mesenchymal origin

While tuberous sclerosis is a rare disease, the correlation of the clinical picture with the striking radiographic findings will usually provide the correct diagnosis

The authors are indebted to Dr Francis W Porro for the pathological interpretation and photomicrograph appearing in this paper

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[11] Inglis, K Relation of renal lesions to cerebral lesions in tuberous sclerosis complex Am J Path , 30 739-757, 1954

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MALIGNANT MESENCHYMOMA OF THE KIDNEY CASE REPORT

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Malignant tumors composed of mesenchymal tissue within the kidney are most unusual and quite rare[1] A similar tumor, the renal hamartoma, is also unusual, and differs in that it is classified as a benign neoplasm and shows no cellular evidence of malignancy

CASE REPORT

A 46-year-old white man entered the hospital in April 1956 complaining of intermittent sharp left flank pain of 10 years' duration The pain had become much more severe during the 2 weeks preceding his admission, and occasionally had radiated to his left groin and testicle He had noticed red blood in the urine coinciding with the attacks of pain He had lost weight during the past year, in spite of a satisfactory appetite Past history, family history and system review were noncontributory

Physical examination revealed an urticarial skin rash believed due to penicillin, a left varicocele and a right spermatocele The remainder of the physical findings were normal No mass was palpable in the left flank or abdomen

The urine was clear with a specific gravity of 1 022, an acid reaction and a trace of albumin Bladder and kidney urine cultures were negative in 48 hours The blood Kahn was negative The nonprotein nitrogen was 30 5 mg per cent and the creatinine was 1 4 mg per cent The hematocrit on admission was 42 per cent, the white blood count was 9,750 with a normal differential count A chest x-ray was interpreted as normal Retrograde pyelograms showed the left kidney to be enlarged (fig 1) On injection of contrast material, there was a reticulated appearance of the contrast material, with a filling defect of peculiar pattern A calcified area was also noted in the lower pole of the left kidney At the time of the retrograde pyelograms, phenolsulfonthalein dye concentrated well bilaterally in 15 minutes

Under general anesthesia, a left nephrectomy was performed through an 11th intercostal incision on April 16, 1956 A large renal tumor, the size of a grapefruit, was detected at the lower pole There was an extensive infarct of the upper pole The tumor was adherent to the peritoneum and perirenal fascia, although there was no gross evidence of tumor extension On sectioning the kidney, multiple tumor masses were noted which were secondary to the large, apparently primary tumor

Pathologic diagnosis (Dr Thomas C Laipply) "The specimen submitted for pathologic examination (fig 2) consists of a left kidney with attached portion

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Read at annual meeting, North Central Section of American Urological Association, Cleveland, Ohio October 3-5 1956

[1] F K Mostofi, Armed Forces Institute of Pathology Personal communique, May 1956

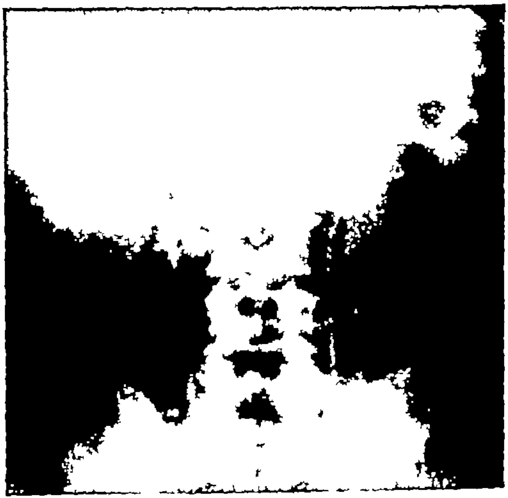

FIG 1 Bilateral retrograde pyelogram shows reticulated filling defect on left

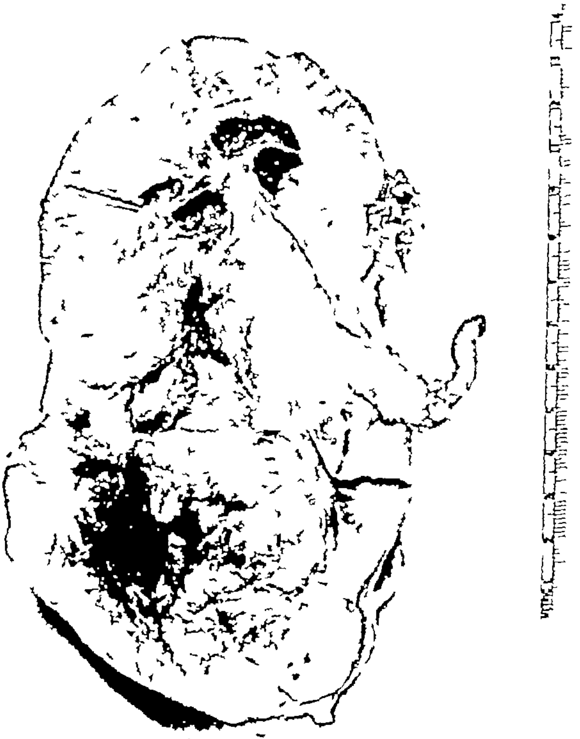

FIG 2 Cut surface of kidney shows tumor mass occupying lower pole Note area of infarction in upper pole

of ureter, which weighs 858 gm and measures 17 by 11 by 10 cm The capsule strips with moderate difficulty to reveal a large, diffusely-lobulated, yellowish orange tumor which replaces the entire lower pole of the kidney and invades the surrounding fibroadipose tissue In addition, in the region of the lower pole are

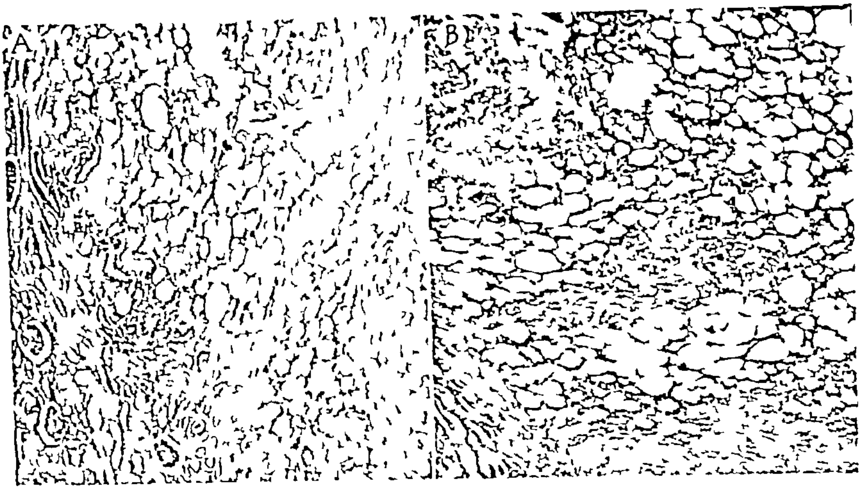

Fig 3 A, note tumor invading normal kidney substance B another area of invasion and apparent malignant nature of tumor cells

numerous small tumor nodules, which are pale yellow, friable and papillary in nature The renal parenchyma in uninvolved areas measures 2 3 cm in thickness, with a cortex of 1 0 cm thickness The tumor has greatly distorted and displaced the lower calyces The opposite pole of the kidney is dark blue and finely granular, and on cut section shows an enormous wedge-shaped area which occupies the entire upper pole The portions of renal pelvis not involved by tumor are lined by wrinkled, pale gray mucous membrane which extends into a portion of ureter, which measures 11 0 cm in length At one point, tumor tissue extends through to the perinephric fibroadipose tissue and presents a broken, pigmented surface four centimeters in diameter

'Microscopic sections (fig 3, 4) reveal kidney tissue which is composed of the usual glomerular and tubular elements, in which are seen occasional foci of tumor cells, which are characterized by a necrotic pattern with loss of cellular identification These foci are surrounded by inflammatory cells The region of transition between tumor and normal kidney shows an abrupt change with loss of renal architecture and replacement by signet-ring fat cells, throughout which are strands and sheets of tumor cells These cells have a more or less spindle-shape, but show marked pleomorphism of nuclear and other cellular components The nuclei vary in shape from small spindle types to large, oval to globular configurations Numerous mitotic figures are seen The unusual feature of this tumor is the pattern in which well-formed fat cells are interspersed with irregular-appearing eosinophilic tumor cells Additional sections through small portions of tumor reveal degenerative necrotic tumor cells In one section, a large thick-walled vascular channel is present in the center of which are fragments of necrotic tumor tissue Diagnosis Malignant mesenchymoma (lipoleiomyosarcoma) of kidney and perinephric fibroadipose tissue with metastases to renal cortex Recent infarct of kidney "

DISCUSSION

The term "malignant mesenchymoma" has been applied to those tumors of the soft tissues of mesenchymal origin, which are composed of tumor cells differentiating into two or more unrelated malignant forms If a lymphosarcoma, for example, happens to contain adult bone or cartilage in its framework, this does not indicate another malignant element But, when tumors are composed of two or more unrelated malignant elements, such as leiomyosarcoma and hemangioma, then it is necessary to recognize the complexity of composition by another name

McFarland,[2] in his article on mixed tumors of the urogenital region, believes that these tumors result from dysontogenesis By definition, dysontogenesis expresses accidents of development that may be followed by malformation or tumor occurrence The tumors of this group have no standards of histological structure Some appear as simple tissue tumors and others are compounded of several tissues and are correspondingly complex The cells of these tumors may be dislocated embryonal cells, which may be suppressed and extinguished, or may continue to live and complete their own differentiation in the abnormal environment Since they retain the potentialities of future development into normal tissue, so also they possess the potentiality of tumor development The histological variation of the tumors and the differing proportions of their tissues result from the kind of cells dislocated and the ease with which their evolution is effected in the abnormal environment in which they find themselves

In describing these tumors, McFarland points out the great divergence of appearance and structure Many are very soft, edematous, myxoid, polypoid and cystic, while others are firm, dense, fibroid, muscular, cartilaginous and even osseous

Although many of these dysontogenetic tumors are found in the urogenital tract especially within the urethra, vagina, cervix and bladder, Stout[3, 4] has reported 8 cases of mesenchymomas from other body regions These include tumors from gluteal muscle, rectus femoris muscle, posterior thigh, the lateral aspect of the neck, pleura, liver and the subcutaneous region of the leg Stout also believes that most mixed mesenchymal tumors probably are initiated as a result of developmental faults, but states that there is some support for metaplasia as a basis Stout's eight cases are alike only in the fact that all are actually or potentially malignant, all are mixed tumors, compounded of cells and tissues of a variety ordinarily derived from primitive mesenchyme, not one of these is a standard variety sarcoma, and each, if designated according to tissue content, would have to receive a different compound name

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McFarland, J Dysontogenetic and mixed tumors of the urogenital region Surg, Gynec & Obst, **61** 42–57, 1935

[3] Stout, A P Tumors of the soft tissues Armed Forces Institute of Pathology, F 5—pp 79–80, 1953

[4] Stout, A P Mesenchymoma, the mixed tumor of mesenchymal derivatives Ann Surg, **127** 278–290, 1948

A mixed tumor (lipo-osteo fibrosarcoma) of the spermatic cord was described by Dreyfuss[5] in 1940. His patient had noted a pea-sized intrascrotal nodule for 14 years which began to grow 8 months prior to surgery.

Capsulomas of the kidney and the renal lesions of tuberous sclerosis are benign mixed tumors, which usually contain fibrous connective tissue, smooth muscle and adipose tissue. We have found no reports of malignant mesenchymomas of the kidney in recent literature. However, there are several case reports of mixed mesenchymal tumors of the kidney, which come under the heading of renal hamartomas and which are similar to the tumor described in this paper with the exception that there are no microscopic evidences of malignancy in the tissue elements of the hamartoma. The case which most closely resembles our tumor grossly, and yet is benign microscopically, was that published by Hulse and Palik.[6] This was a case of a 42-year-old woman with known tuberous sclerosis and a tumor of the lower pole of the left kidney removed by nephrectomy. Microscopically, there were numerous dysplastic formations in the cortex, medulla and perirenal tissue, composed of normal adipose tissue and interlacing fasciculae of normal fibrous tissue. There were no mitoses in any of the cellular elements of these tumors. The diagnosis was hamartoma of the kidney. Hulse and Palik also reported a case of a 59-year-old woman who had a kidney removed. There was a tumor 2.0 inches in diameter found bulging from the surface of the kidney along the lateral border in the upper third. The tumor was composed of a dysplastic conglomeration of adipose tissue, blood vessels, fibrous tissue and smooth muscle. Fibroblastic tissue in some areas was loosely knit and mesenchymal in type, composed of spindle cells having small to moderately large oval hyperchromatic nuclei. Several similar small dysplastic foci were scattered throughout the cortex.

According to Rusche,[7] a renal hamartoma is a lesion formed by normal tissue elements, which are abnormal only in their quantitative value. As of 1952, there were 52 cases of renal hamartoma recorded at the Armed Forces Institute of Pathology. All of these patients were males, 44 were discovered at autopsy and eight prior to death. Rusche believes that renal hamartomas characteristically lack mitotic figures, are noninvasive, do not metastasize and act and look benign. Patients with renal hamartomas typically have no symptoms localized to the kidney, although they may have a renal mass and hematuria. One-half of patients with tuberous sclerosis have multiple benign tumors of the kidney, described as renal hamartomas.

SUMMARY

The case which we present of malignant mesenchymoma of the kidney is similar to, but not exactly like the descriptions in the literature of renal hamartomas. Our tumor contains elements of sarcomatous, smooth muscle tissue with definite mitotic figures and marked pleomorphism and hyperchromatism There was also capsular invasion and adhesions of the kidney to surrounding perirenal fascia and peritoneum It is too soon to know whether or not this patient has been cured of his disease If, at a future date, distant metastases do develop, there will be no question but that we are dealing with a malignancy from a clinical as well as from a pathological point of view If, however, the patient remains cancer-free, there will be some speculation as to whether this tumor was a renal hamartoma with focal cellular malignant change, or whether it should be classed as a malignant mesenchymoma which has been completely removed

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[5] Dreyfuss, M. L. and Lubash, S.: Malignant mixed tumor of spermatic cord. J. Urol., 44: 314–324, 1940.

[6] Hulse, C. A. and Palik, L. E.: J. Urol., 66: 506–515, 1951.

[7] Rusche, Carl: J. Urol., 67: 823–831, 1952.

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RENAL TUBERCULOSIS SIMULATING HYPERNEPHROMA

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The urographic manifestations of tuberculosis are extremely variable ranging from negative minimal findings to that of a kidney which has undergone autonephrectomy.

In 1941 Bugbee reported on the first case of tuberculoma of the kidney in which the urographic and gross findings were compatible with a tumor of the renal pelvis. The patient complained of increased frequency of urination and a diagnosis of tuberculosis was made preoperatively. That same year Eggs reported one case of tuberculoma of the kidney having a calcified solitary tubercle. Three years later Wang and Verges-Flaque described another case of tuberculoma of the kidney. In this case there was a conglomeration of tubercles resembling and having the appearance of a tumor.

Tuberculoma of the kidney is defined as a conglomerate of caseous tubercles, usually solitary, attaining such size as to have the appearance of a tumor.

In view of the paucity of the literature in relation to this most unusual condition and as the radiological findings may be extremely misleading, we believe it to be of interest to add another case to the medical literature.

CASE REPORT

AU (HR 117 862), a 33-year-old WAC was admitted to the 2151-1 U. S. Army Hospital on December 1953, because of generalized malaise, backache, chills and fever of 3 days duration. The review of symptoms was not significant and the past history was noncontributory. There was no family history of tuberculosis and she had never been in close contact with any one who had the disease.

The physical examination revealed a well developed, well nourished white woman in no acute distress complaining of moderate tenderness in the right costovertebral angle. The impression of the admitting physician was that of right acute pyelonephritis.

The laboratory studies revealed a red blood cell count of 3.75 million, hemoglobin of 12.5 gm. and a white blood count of 11,750 with a normal differential count. On the urinalysis a 1 plus albumin with numerous red and white blood cells per high power field were found and Gram stain of the urine sediment revealed gram positive cocci.

The patient was given 1 gm. 4 times daily of gantrisin and 600,000 units of penicillin but she continued to have a septic temperature for 3 days. The urine culture yielded Streptococcus alkaligenes faecalis as a predominant organism resistant to penicillin, aureomycin, and terramycin, slightly susceptible to streptomycin and bacitracin and susceptible to chloromycetin. The tuberculin test was interpreted as strongly positive.

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The patient was then given 250 mg chloromycetin 4 times daily followed by prompt subsidence of fever within 24 hours and a marked improvement in her general condition Another urine culture several days later was sterile but persistent microscopic hematuria was observed

A plain urogram revealed an enlarged right renal shadow with irregular contour at the inferior pole An excretory urogram was made with diodrast and prompt excretion of the opaque medium by both kidneys was observed There was an upward displacement of the right renal pelvis by a soft tissue shadow mass arising from the inferior pole of the kidney, and the inferior calyx appeared to be eroded A cystoscopic examination was performed next day The bladder was normal, the ureteral orifices were of normal size, shape, and spurted clear urine Ureteral catheters were readily passed to the renal pelves and urine specimens collected for acid fast stain and cultures The latter were reported negative for acid fast organisms The retrograde pyelogram (fig 1) confirmed the findings of the excretory urogram The renal function tests were within normal limits and a roentgenogram of the chest and skeletal system failed to reveal any evidence of pathological changes

An exploration of the right kidney was deemed advisable in view of the urographic findings and persistent microscopic hematuria A right nephroureterectomy was performed

Pathologic report (R C Harsh, pathologist) Specimen 2, AAML S-667253 "The gross specimen consists of a kidney which weighs 155 gm and measures 12 by 7 by 4 cm The capsule strips easily from the surface of the kidney save for a tumor mass on the lower pole of the kidney The superior pole and mid portion of the kidney have a pale yellowish brown, moderately firm mass of

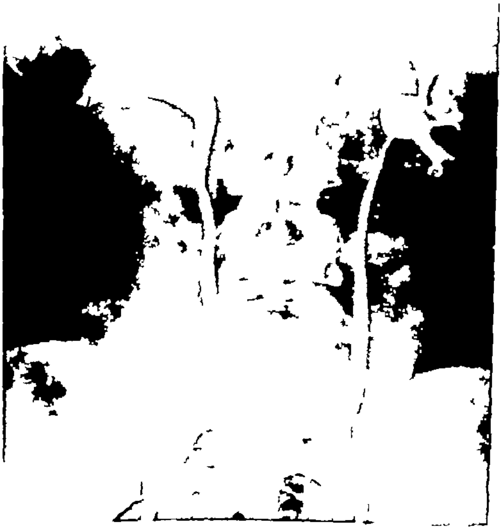

FIG 1 Retrograde pyelogram revealing obliteration of inferior group of calyces of right kidney and upward displacement of renal pelvis by mass in inferior pole of kidney

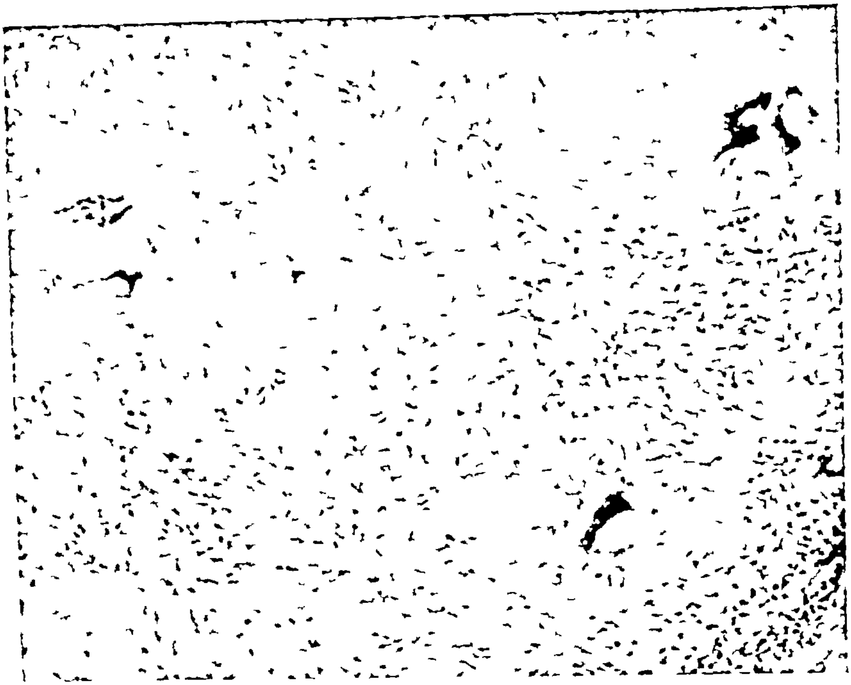

FIG 2 Photomicrograph through section of tuberculoma × 430

tissue which extends into the adjacent renal parenchyma in an irregular manner The tumor extends into the wall of the kidney pelvis but grossly does not extend into the pelvis The tumor mass measures 4 by 4 by 3 cm

"On section the surface is pale, yellowish brown firm, irregular, and slightly bulging The uninvolved section of the kidney shows a normal cortex and medulla which are demarcated from each other The ureter is attached to the kidney and its proximal portion is slightly dilated and the mucosal surface is pale pinkish gray soft and wrinkled There are occasional small, poorly defined slightly raised pale gray nodules present in the mucosal surface

Microscopic study (fig 2) Sections of the lesion show complete replacement of the kidney parenchyma by a poorly defined area of conglomerate tubercles The tubercles are composed of lymphocytes, fibroblasts, epithelioid cells and giant cells within a stroma of connective tissue fibrin The renal pelvis and ureter are involved in the process Acid fast bacilli were identified Diagnosis Conglomerate caseous tuberculosis of the right kidney, tuberculosis of the renal pelvis and ureter "

In view of the pathological findings the patient was recalled and hospitalized Three consecutive urine cultures for acid fast and guinea pig inoculations were reported negative The studies were done to rule out the possibility of involvement in the remaining kidney and ureter The patient was given streptomycin 1 gm twice a week, para-amino-salicylic acid 15 gm daily and isoniazid 100 mg 3 times a day The patient received that treatment for 1 year She has continued to do well and repeated urine cultures for acid fast bacilli have been negative

CONCLUSIONS

Another case of tuberculoma of the kidney is reported

The pyelographic findings were those of renal tumor

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WILMS' TUMOR WITH URETERAL METASTASES EXTENDING INTO THE BLADDER

JOHN P. WATKINS

A Wilms' tumor with extension down the ureter into the bladder is apparently a rather unusual phenomenon. There is no medical library here in southern Nevada so that a comprehensive review of the literature to determine the number of previously reported such cases is impossible. Garrett and Mertz[1] in reporting on Wilms' tumors in children, mentioned the only reference I could find concerning such a metastasis; this was reported in the JOURNAL OF UROLOGY (vol. 46, 1941, Mertz, Howell and Hendricks). Campbell's[2] extensive bibliography for his chapter on "Tumors of the Urogenital Tract in Children" does not include a reference to such an extension and he also makes no mention of this in his discussion of Wilms' tumors. Also a review of the JOURNAL OF UROLOGY from 1949 to the present time reveals no reported cases or mention of such cases except the one aforementioned. Thus this phenomenon would seem to be at least rare and interesting enough to report when discovered and the following is a case history of such an occurrence.

An 11-month-old white boy was seen by the author for the first time on June 14, 1955 because of a mass in the right upper quadrant and gross hematuria.

History obtained from the mother revealed the occurrence of gross hematuria approximately four months previously that lasted for about two weeks. About four weeks before examination, a repair of a right inguinal hernia and a right hydrocelectomy were performed. No abdominal mass was discovered on this admission and although the occurrence of the gross hematuria in the past was known, no urological investigation was performed during this admission. About ten days prior to the present admission gross hematuria was again noted, and a few days later, on examination, a large right upper abdominal mass was discovered.

Physical examination revealed a well developed, well nourished, alert 11-month-old white boy with a visible protuberance of the right upper abdomen. This was a somewhat ballotable nontender mass approximately seven to eight centimeters in diameter, and extended somewhat below the level of the umbilicus. The remainder of the abdomen was negative except for a recent right inguinal incisional scar. The scrotal contents were normal. The remainder of the examination was not remarkable.

An intravenous urogram was attempted but no suitable vein could be found.

Cystoscopy and bilateral retrograde pyelograms were then performed under open drop ether anesthesia. Immediately on viewing the area of the right ureteral orifice a pedunculated tumor mass was seen protruding from the lateral side of the right ureteral orifice. This was a reddened, edematous mass of tissue which

Accepted for publication September 27, 1956.

[1] Garrett, R. A. and Mertz, H. O.: Wilms' tumor in children. J. Urol., 70: 694, 1953.

[2] Campbell, Meredith: Clinical Pediatric Urology. Philadelphia: W. B. Saunders Co., 1951.

seemed to be on a relatively small pedicle It was friable and bled easily and appeared cystoscopically to be malignant

After some difficulty a No 4 ureteral catheter was inserted up the right ureter for a distance of 10 cm and a right retrograde pyelogram and ureterogram revealed a markedly distorted and compressed pelvis and calyces at the upper medial portion of a large mass The ureterogram revealed a tortuous, dilated ureter with filling defects all the way down A left retrograde pyelogram and ureterogram were completely normal (fig 1)

The initial impression was a Wilms' tumor with extension down the ureter to the bladder (It was realized that this would be an unusual phenomenon) Papillary transitional cell carcinoma was kept in mind but was not suggested by the appearance of the pyelogram A neuroblastoma seemed an unlikely possibility

Laboratory studies revealed a normal blood count and urinalysis was negative except for 25 to 30 red blood cells per high power field

A chest film revealed no metastases

It was decided to do immediate exploration and resection to be followed by x-ray radiation therapy On June 16, 1955, through an ordinary right flank incision later extended downward, the right kidney and dilated upper ureter were exposed and a right nephroureterectomy performed along with a cuff of bladder On exploring the interior of the bladder the pedunculated mass of tissue was found lying loose within the bladder, apparently having sluffed off following the cystoscopy No evidence of metastases to the liver, renal pedicle, aortic nodes, or local perirenal extension was found

Postoperatively the infant did well and was discharged 5 days later and flown to Children's Hospital in Los Angeles, California, where a total of 6,000 r divided into three ports was given over a period of 47 days

Subsequently, except for a somewhat depressed white blood count and some nausea due to the radiation therapy, the patient has done remarkably well and interval chest films and other examinations have been negative for recurrence or metastases

Pathology report (J R Fouts, M D , pathologist, Southern Nevada Memorial Hospital) "The gross specimen is a right kidney and ureter with a small segment of bladder attached and separately a small piece of pink and dull red-brown tissue from the bladder The kidney measures 12 by 11 by 9 cm and weighs 585 gm The capsule is intact and not remarkably adherent A 4 5 by 2 5 by 2 5 cm zone at the upper pole has the appearance of renal parenchyma Remainder of the mass is a well circumscribed neoplasm Part of the neoplasm is pink-grey and firm and part yellow and red and soft Renal pelvis is dilated Neoplasm extends into calyces and pelvis and obstructs orifice of ureter Ureter measures 10 5 cm in length and from 12 to 14 mm in circumference Neoplasm is in lumen and attached to mucosa of proximal part of ureter Attached segment of bladder measures 2 0 by 1 5 cm , is normal in color and consistency Separate segment of bladder measures 4 3 by 1 5 by 1 0 cm Part of mucosa appears polypoid "

Microscopic examination "Neoplasm in kidney, extending into ureter and

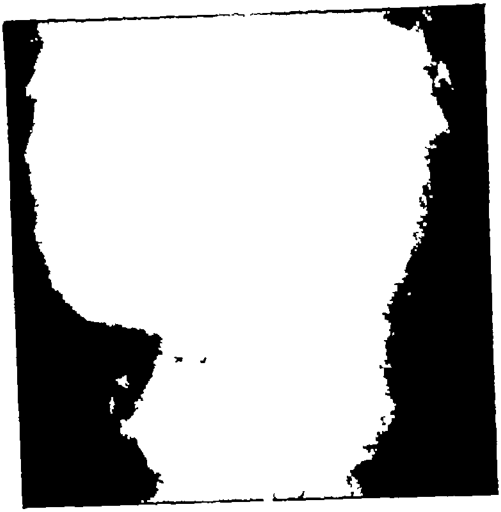

Fig 1

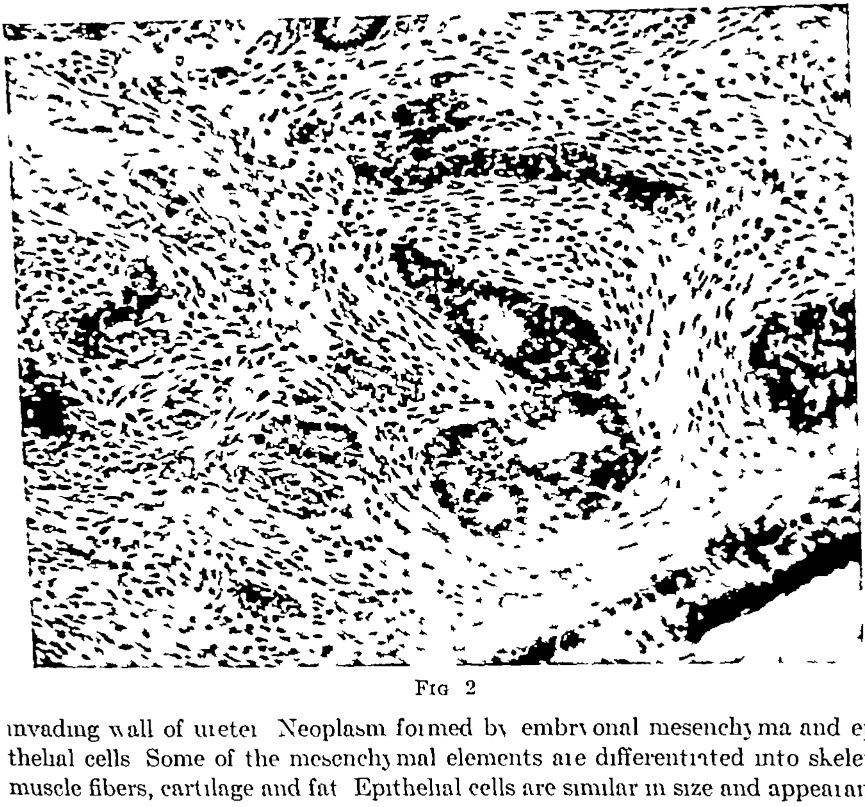

Fig 2

invading wall of ureter Neoplasm formed by embryonal mesenchyma and epithelial cells Some of the mesenchymal elements are differentiated into skeletal muscle fibers, cartilage and fat Epithelial cells are similar in size and appearance to lymphocytes Epithelial cells are arranged as nests, cords, tubules and multiacinar structures No mitoses Large areas of necrosis in tumor Segment of bladder attached to ureter is not involved Separately submitted piece of tissue shows necrotic tumor No intravascular invasion by tumor "

Diagnosis Nephroblastoma (Wilms' tumor) with extension into ureter and metastatic implantation in bladder (fig 2)

SUMMARY

An unusual case of Wilms' tumor in an infant with extension down the ureter into the bladder is presented No evidence of recurrence or metastases is present 15 months following surgery and radiation therapy

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PROLAPSING URETEROCELE AS A CAUSE OF HEMATURIA IN AN INFANT

MAJOR A. M. WILEY*

Ureterocele, or cystic enlargement of the vesical portion of the ureter, is an uncommon urological condition occurring typically in adult females. It is bilateral in 10 per cent of cases. The enlargement, the pathology of which has been the subject of a good deal of discussion, is the result of congenital or acquired narrowing of the ureteric orifice. There are two forms of the condition: 1) Mucus form, in which the cyst is formed of vesical mucosa and 2) prolapsing form, where the cyst contains a layer of muscle in its wall and is assumed to be an intravesical prolapse of the entire ureter.

Common symptoms resulting from ureterocele are recurrent ureteric pain, renal pain, hematuria and dysuria.

Lechler (1834) was the first to describe the condition, which he discovered in a 3-month-old infant. English (1938) collected 15 additional cases while Lipmann Wolf (1898), Grosglik (1901) and Cohn (1904) were the first surgeons to diagnose and treat the condition by conventional means. Blum (1920), reviewing 100 cases, was the first to adequately describe the nature of ureterocele while Gutierrez (1939) gave a detailed account of it, describing nine different varieties. Macpherson (1942) added a further case and discussed the pathology.

A female infant suffering from ureterocele recently came under the care of Army Medical Services in Kluang, Johore and a perusal of the available literature suggested that in this instance the mode of presentation of the condition was unique. The patient perished and postmortem study was possible only because amongst this Muslim community the child happened to be a Chinese orphan, and a girl, purchased at very low cost by its guardians who abandoned it when it was seen to be ill.

CASE REPORT

Khoo Siew Bee was an orphan aged 2 months who had apparently been quite healthy until the date of admission on December 13, 1955. She then vomited and passed a number of loose motions. On examination she was found to be dehydrated. Her skin was covered in tiny red papules and she appeared to have been neglected. Temperature was normal. Some moist sounds could be heard at the right base and the abdomen was distended and tympanitic. Bowel sounds were heard. The vulva was discolored, the urethra was patulous and appeared to be partially prolapsed. Her urine was streaked with fresh blood and mucus. A provisional diagnosis of gastroenteritis was made associated with general neglect and vulvitis. Her condition gave rise to little alarm and she was treated by regulated oral feeds. Streptomycin was given for her perineal "infection." She continued to pass blood stained urine and died suddenly a week later.

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bladder attached to ureter is not involved Separately submitted piece of tissue shows necrotic tumor No intravascular invasion by tumor "

Diagnosis Nephroblastoma (Wilms' tumor) with extension into ureter and metastatic implantation in bladder (fig 2)

SUMMARY

An unusual case of Wilms' tumor in an infant with extension down the ureter into the bladder is presented No evidence of recurrence or metastases is present 15 months following surgery and radiation therapy

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There can be no doubt that the narrowing of the right ureteric orifice was congenital A cystic condition of the kidneys has been noted by Williams in patients who suffer from lower urinary obstruction starting in fetal life, but the association between cortical cysts of the kidneys and congenital stenosis of the ureter is obscure It is presumed that the condition of the left ureter was the result of chronic obstruction at the internal urethral orifice brought about by the prolapsing right urethrocele In conclusion a note regarding treatment This would have been of little avail in this case where renal dysfunction was already extensive In suitable cases a urethrocele may be widely incised by the diathermy Gutierrez thoroughly describes the treatment of urethrocele

My thanks are due to Lt Col J Irvine, O B E, O C British Military Hospital, Kluang for permitting me to investigate and treat the patient

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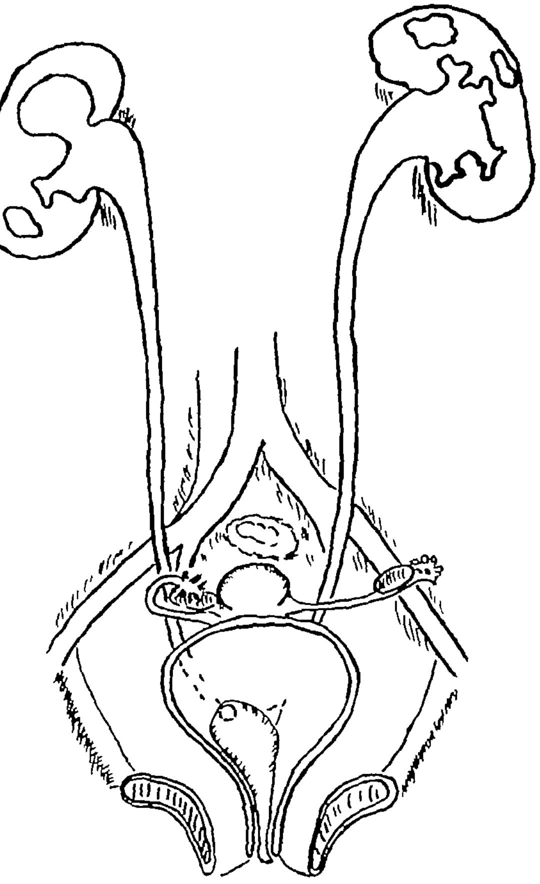

FIG 1 Diagram of postmortem appearances Prolapsing ureterocele, dilated ureters and pelvic hydronephrosis of kidneys containing cortical cysts

Postmortem findings The abdomen was opened by a midline incision The bowels appeared to be normal Two enormously distended ureters were seen extending from a small and thickened bladder to apparently normal kidneys When the bladder was opened it was found to be partially filled by a delicate mucous ureterocele which extended out through the external urethral orifice thereby giving rise to the erroneous diagnosis of prolapsing urethra The intramural portion of the right ureter was enormously dilated The left ureteric orifice was in its normal position and was of normal appearance Both renal pelves were distended Both kidneys contained a number of large cortical cysts One of these was in communication with the renal pelvis on the right side See figure 1

COMMENT

The rarity of this condition in infants and the unusual mode presentation lead to a failure in diagnosis Vulvitis associated with neglect is not uncommon among infants seen here, added to which it is the common practice of local herbalists to apply irritant concoctions to any diseased part, this procedure was indeed suspected in this case

There can be no doubt that the narrowing of the right ureteric orifice was congenital. A cystic condition of the kidneys has been noted by Williams in patients who suffer from lower urinary obstruction starting in fetal life, but the association between cortical cysts of the kidneys and congenital stenosis of the ureter is obscure. It is presumed that the condition of the left ureter was the result of chronic obstruction at the internal urethral orifice brought about by the prolapsing right urethrocele. In conclusion a note regarding treatment. This would have been of little avail in this case where renal dysfunction was already extensive. In suitable cases a urethrocele may be widely incised by the diathermy. Gutierrez thoroughly describes the treatment of urethrocele.

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URETERAL IMPLANTATION CLINICAL EXPERIENCES

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This paper is presented to record the clinical experiences, impressions and conclusions of men working chiefly in private practice away from medical schools The indications found, the methods employed, the advantages, and results are discussed The methods thought to be best at present and possible improvements are considered

LITERATURE

The literature has been reviewed by others (Cordonnier) The possible methods of ureteral implantation include 1) uretero-ureteral (Prentiss and Mullenix) (fig 1, *A*), 2) contralateral ureteroureteral (Slutsky), 3) ureteroneocystostomy (Prentiss and Mullenix) (fig 2), 4) cutaneous ureterostomy (Zenaim), 5) ureterostomy in situ or tube ureterostomy (Prentiss and Mullenix) (fig 3), 6) cystoureteroplasty (vesical flap ureteroplasty) (Conger and Rouse) (fig 4), 7) uretero-ileostomy (Cordonnier) (fig 5), 8) ureterosigmoidostomy (Coffey '28), 9) uretero-cecal-ileostomy (Merricks and Gilchrist), 10) isolated rectal bladder with colostomy (Paull and Hodges), 11) Boyce-Vest procedure (recto-vesical diverticulum), 12) Lowsley isolated rectal bladder with intrasphincteric sigmoid perineal colostomy, 13) ureteroileocystostomy (substitution of ileum for ureter) (Moore, Weber, Woodward, Moore and Goodwin), 14) wet colostomy (ureterosigmoid-colostomy) (Brunschwig), 15) reversed seromuscular ileal grafts (Shoemaker)

METHODS

The authors have employed the following methods 1) uretero-ureterostomy (fig 1, *A*), 2) ureteroneocystostomy (fig 2), 3) cutaneous ureterostomy, 4) cystoureteroplasty (fig 4), 5) ureterosigmoidostomy, 6) uretero-ileostomy (fig 5), and 7) ureterostomy in situ (fig 3)

Ureterocolostomy was performed by the techniques of Coffey 1, Coffey 2, Coffey 2 combined with mucosa-to-mucosa interrupted suture (fig 6), the Flocks, the Nesbit, the Mathisen, and the Cordonnier methods

CLINICAL MATERIAL

The operations were done on private patients by the authors Charity patients of the San Diego County General Hospital were treated by the residents and attending urologists including the authors

This study is based on experience with implantation of 168 ureters in 105 patients Of these there were 79 private and 26 charity patients The subjects have been grouped into two divisions group 1, those presenting primarily open surgical injury to the ureter, requiring disposition, and group 2, those needing ureteral implantation as a part of treatment of a primary disease There were 34 patients presenting 42 injured ureters in the first group, and 71 patients pre-

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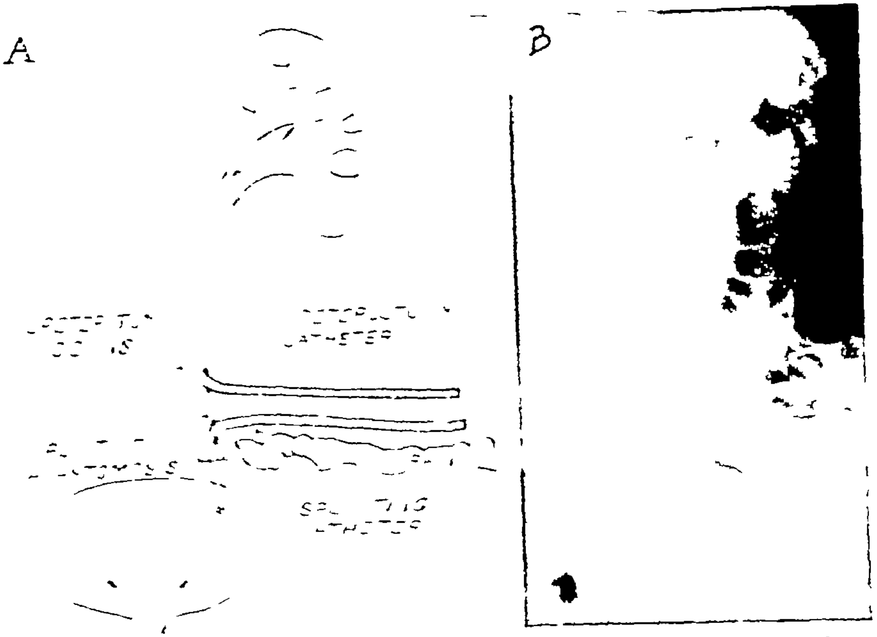

FIG 1 A Ureteroileal anastomosis illustrating [illegible] ureteral splint diversion and drain, B Ureteroileal end-to-end anastomosis. Note splint and ureterostomy. Fi[illegible] present

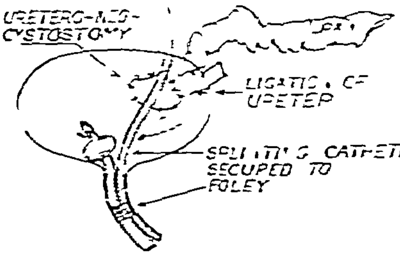

FIG 2 Diagram showing technique of ureteroneocystostomy

senting 126 ureters for implantation in the second The first group presented 23 5 per cent malignancies and 96 7 per cent were females In the second group 69 per cent had malignancies of pelvic organs and of these 65 per cent were males The average age of group 1 was 45.2 years and of group 2 was 51 4 years

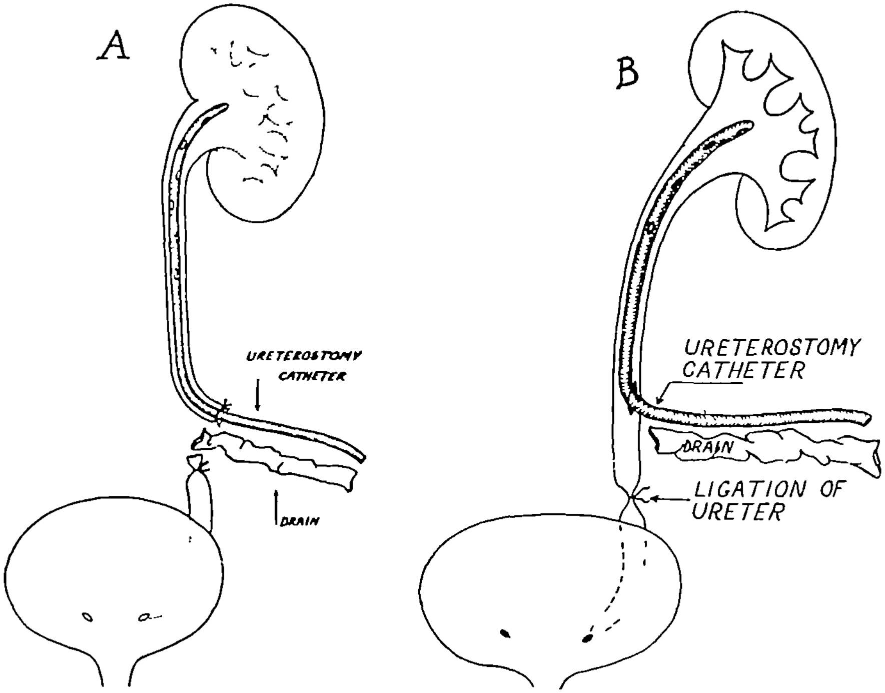

FIG 3 *A*, diagram illustrating ureterostomy in situ when abdomen is open *B*, ureterostomy in situ, or tube ureterostomy through extraperitoneal muscle splitting incision

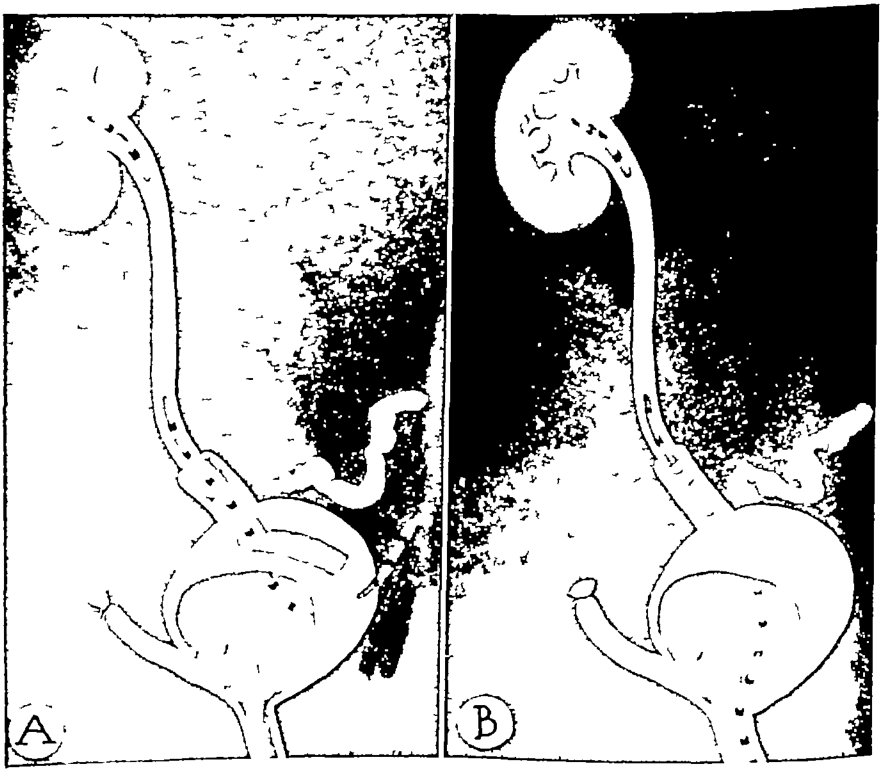

FIG 4 Technique of vesical flap cystoureteroplasty *A* creation of flap *B*, anastomo complete

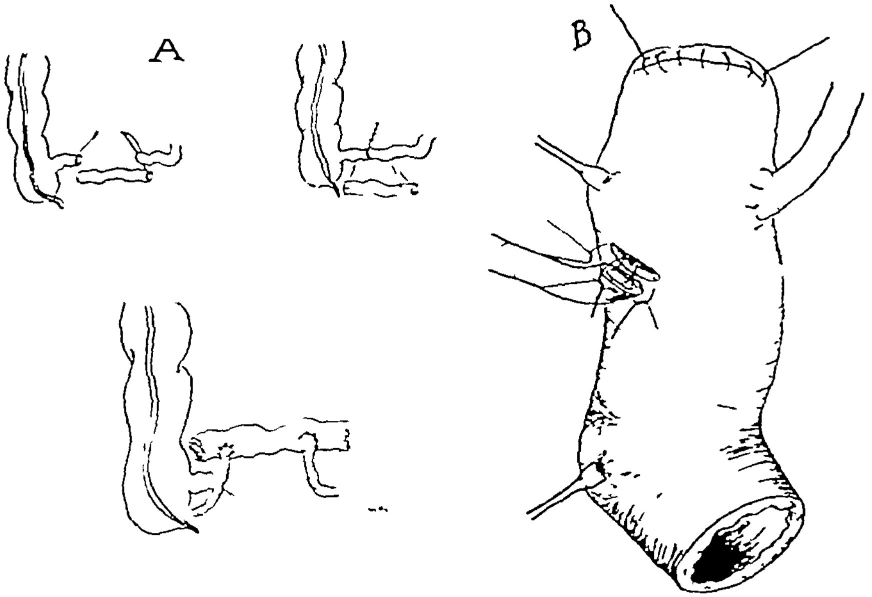

FIG 5 A, sketch of ureteroileostomy technique B, technique of ureteroileal anastomosis

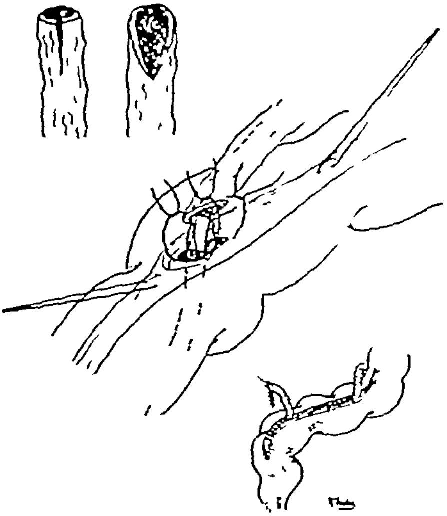

FIG 6 Coffey 2 combined with mucosa to mucosa interrupted suture (authors' technique)

The indications for the ureteral operation were the usual for the problems presented in both groups

RESULTS

Results are classified as good, fair or poor, on the basis of the degree of infection, hydronephrosis, uremia, acidosis and/or hyperchloremia Results are presented separately according to the two groups, and according to method of implantation

The patients presenting primary surgical injury to the ureter (group 1) enjoyed

83 8 per cent good results and none died Techniques employed and recommended will be described below

Group 2, those requiring ureteral implantation as a part of treatment of a primary disease, are listed below according to the method employed Only the results of ureterosigmoidostomy are tabulated

Vesical flap or cystoureteroplasty The one patient obtained a good result

Ureteroneocystostomy Malignant disease Six patients, presenting nine ureters for implantation Results were 50 per cent good, 16 6 per cent fair, and 33 4 per cent poor, and none died Benign disease Two patients, presenting three ureters for transplant Good results were obtained in all

Ureteroileostomy Three patients, presenting six ureters for implantation One patient had a malignant condition All obtained good results, although the ureters were implanted twice in one patient

Cutaneous ureterostomy Malignant disease Five patients presented six ureters for implantation Results were 60 per cent good and 40 per cent died, but had non-surgical causes of death Benign disease There were seven patients, presenting nine ureters Results were 42 8 per cent good, 28 6 per cent fair, 28 6 per cent poor and none died

Ureterosigmoidostomy Benign disease Eight patients presented 16 ureters for transplant Results were 50 per cent good, 12 5 per cent fair, 37 5 per cent poor, including one death Malignant disease Thirty-eight patients with 71 ureters for implantation Results were 38 per cent good, 32 per cent fair, and 30 per cent poor, including six deaths

Table 1 presents the details of results with various methods of ureterosigmoidostomy Some patients had more than one type of procedure, hence the excess number listed in the table

Study of tables 2 and 3 reveals the incidence of complications in ureterosigmoidostomy Some, as acidosis, hyperchloremia and uremia, are due to altered physiology of absorption, perhaps aggravated by obstruction to the ureters and urinary infection All methods produced these changes, but the Coffey 2 method

TABLE 1 *Results Ureterosigmoidostomy*

Procedure		Good (per cent)	Fair (per cent)	Poor (per cent)	Mortality (percent)
Cordonnier	5	0	20	80	20
Nesbit	7	14 2	42 9	42 9	14 3
Mathisen	1	100	0	0	0
Flocks	3	0	33 4	66 6	66 6
Coffey 1	4	0	50	50	0
Coffey 2	12	33 3	33 3	33 3	8 3
Coffey 2 combined	23	60 7	30 7	8 5	0
Total	55	38 0	32 0	30 0	12 7

Autopsy rate of P O deaths, 82%

Average age, 51 4 years

Age span, 8 years to 79 years

TABLE 2 *Surgical complications Ureterosigmoidostomy*

Procedure		Fistula per cent	Intestinal Obstruction per cent	Abscess per cent
Cordonnier	5	40	20	20
Nesbit	7	14	0	14
Mathisen	1	0	100	0
Flocks	3	33 3	0	33 3
Coffey 1	4	25	0	0
Coffey 2	12	8 4	8 4	33 4
Coffey 2 combined	23	8 6	8 6	21 5
Total	55	7 6	3 3	10 8

TABLE 3 *Renal complications Ureterosigmoidostomy*

Procedure		Hydronephrosis per cent	Pyelonephritis (per cent)	Uremia per cent	Acidosis Hyperchloremia per cent	Lithiasis per cent
Cordonnier	5	40	80	80	40	0
Nesbit	7	86	56 4	42 8	71	0
Mathisen	1	0	100	100	100	0
Flocks	3	66 6	100	66 6	66 6	33 3
Coffey 1	4	100	75	50	75	25
Coffey 2	12	41 8	50	58 5	41 8	8 4
Coffey 2 combined	23	47 3	43	34 4	51 6	4 3
Total	55	44 0	44 0	48 4	55 0	8 8

combined with mucosal suture (Leadbetter Leadbetter and Clarke) caused fewer Very possibly this was due to greater experience with this technique

Hydronephrosis and lithiasis were due to anastomotic obstruction Pyelonephritis was felt to be due to obstruction and ascending infection Intestinal obstruction occurred due to small bowel adhesion and internal herniation but once was due to colonic obstruction secondary to fixation bilaterally at the anastomotic sites Abscess and fistula were due to technical errors or ischemic necrosis Dehiscence occurring in two patients, emphasizes the need for strong abdominal wound closure

The Flocks method (side-to-side anastomosis of the intact ureter with intubation and later ligation of the distal ureter) was a dismal failure and was abandoned early The direct end-to-side anastomosis of Nesbit and of Cordonnier gave little better results in the authors' hands The Coffey 1 technique was somewhat better The Coffey 2 method of intubation of the tunnelled anastomosis produced 66 6 per cent acceptable results The authors combined the latter method with mucosa-to-mucosa spatulated end-to-side interrupted suture With the practical method of intubation described below, this last technique produced 91 4 per cent acceptable results This is the best method of ureterosigmoidostomy yet proposed

The over-all mortality was 12 7 per cent Mortality before 1951 was 20 per cent in the private, and 21 per cent in the charity group After 1951 the rate was

5 2 per cent in the former, and 16 6 per cent in the latter patients This indicates the value of experience and the concentration on, and perfection of one method, the combined Coffey 2 method

Autopsies were obtained in 82 per cent of those who died postoperatively The causes of death were uremia, pyelonephritis, electrolyte imbalance, retroperitoneal and pelvic abscess, peritonitis and urinary and/or fecal extravasation, or combinations Some of these are preventable, but the fact remains that urinary diversion to the bowel is a potentially lethal procedure

The operative results as tabulated are very good in two methods However, the final judgment will await long-term survival Excluding surgical deaths, only fifteen of forty patients of this series subjected to ureterosigmoidostomy survive at present For those with malignant disease, the average longevity was 1 81 years with a span of two months to over seven years In the benign group, average survival is 3 55 years, with a span of 1 25 to 10 years This does not appear encouraging, but the authors feel that the more recently treated patients will enjoy much greater longevity

RECOMMENDATIONS GROUP 1 (SURGICAL INJURIES)

The principles involved are 1) early recognition of the injury, 2) preservation of kidney substance, 3) preservation of continuity of the urinary tract, 4) splinting of the injured ureter for adequate time (three to six weeks), 5) temporary diversion of the urine from the site of repair (i e , ureterostomy), and 6) extraperitoneal drainage of the injured area

End-to-end anastomosis Ureteroureteral anastomosis is the method of choice Figure 1, *A* and *B*, is a diagram of the best technique The ureters are mobilized to eliminate tension The ends are freshened by oblique amputation Through a small ureterotomy 2 cm proximal to the division of the ureter, a 6 to 8F fenestrated rubber catheter is passed downward as a splint for the anastomosis and the distal segment A second ureterotomy is made, 2 cm proximal to the first, and a similar catheter is passed upward to the kidney pelvis These catheters are brought out extraperitoneally through a stab incision in the abdominal wall A Penrose drain is placed extraperitoneally through a second stab incision The ureteral ends are sutured together using 000 or 0000 chromic catgut on an atraumatic curved intestinal needle Three or four simple sutures complete the anastomosis None should pierce the mucosa There is no attempt to make the union water-tight The splint, diversion catheter and Penrose drain are left in place at least three weeks The integrity of the anastomosis is checked by injection of a radiopaque fluid before removal of the splint, first, the ureterostomy, second, and the Penrose, last

The method described produces excellent results in establishing continuity and function

Ureteroneocystostomy If the distal ureter does not permit end-to-end anastomosis and if the proximal ureter will reach the bladder without tension, ureteroneocystostomy is preferred (fig 2) The ureter and bladder should be mobilized to eliminate tension The ureteral end is spatulated A 6 or 8F fenestrated rubber catheter is placed in the ureter and passed to the kidney pelvis The bladder is then opened adequately, above the site selected for anastomosis A diagonal stab incision is made at the latter point The ureter and catheter are drawn through and the catheter is passed out through the urethra The spatulate end of the ureter is sutured directly to the bladder mucosa with 000 or 0000 chromic catgut If desired the vesical mucosa may be split permitting edge-to-edge suture The bladder is closed in two layers If it is possible a tunnel of bladder wall is made over the anastomosis but in any case the ureter is secured to the bladder wall as best as is possible A Penrose drain is brought out extraperitoneally The ureteral catheter is left in place 10–14 days and is maintained in position with a No 18 Foley catheter This method of ureteroneocystostomy produces good results

Another technique twice employed in ureterovesical stricture includes wide incision of the intramural ureter with suture of ureteral to vesical mucosa While this certainly eliminates all obstruction it was discarded because it produced troublesome ureteral reflux

Ureterostomy in situ If the distal end of the ureter is lost or destroyed the proximal end is too short for ureteroneocystostomy and the surgical situation precludes more complicated restoration tube ureterostomy is advisable A small urethral catheter placed in the proximal segment of the ureter and exteriorized extraperitoneally will save the proximal ureter and kidney for later study and definitive repair (fig 3 *A*) as by vesical flap ureteroplasty or ureteroileal cystostomy

Delayed discovery of ureteral obstruction in extremely ill patients demands the extraperitoneal insertion of a ureteral catheter in the middle one-third of the ureter (fig 3 *B*) The approach is made through a muscle-splitting incision as in ureterolithotomy A ureterotomy is performed and a suitable urethral catheter is placed in the kidney pelvis This technique solves the problem in extremely ill patients and preserves the ureter and its blood supply for later definitive disposition

RECOMMENDATIONS GROUP 2

This group of 71 patients presented a complicated problem of ureteral implantation because of the primary disease The methods of implantation used by the authors have been listed above, and three have been described the others follow

Cystoureteroplasty This is the method of choice if the distal ureter is lost and the proximal end is too short for ureteroneocystostomy It is preferred to cutaneous ureterostomy ureterosigmoidostomy ureteroileocystostomy and ureteroileostomy The bladder must be pliable and of good capacity to permit bridging of long defects It cannot be used if the proximal stump lies above the common iliac artery

The proximal ureter is mobilized and the end freshened by oblique amputation The bladder is mobilized extraperitoneally The defect to be bridged is measured and superimposed on the partially distended bladder in an oblique fashion A flap is outlined from caudad to cephalad with the base superiorly on the side to be repaired The apex of the flap should be about three centimeters and the base 4 centimeters wide

Scissors dissection of the pedicle graft from the full thickness of bladder wall is completed An 8F rubber Bardam catheter is placed in the kidney pelvis and brought out the urethra The spatulate end of the ureter is sutured to the mucosa of the vesical flap, one centimeter distal to its apex Interrupted 000 chromic sutures are used A tunnel is created from the flap with two layers of running 000 chromic sutures, the bladder being closed with the same sutures The ureteral anastomosis is strengthened with interrupted 000 chromic sutures placed externally (fig 4)

The bladder is drained by a Foley catheter which also fixes the ureteral catheter The wound is drained extraperitoneally by a Penrose wick The catheters and drain should be left in place at least two weeks The integrity of the anastomosis should be checked by the injection of radiopaque fluid before removal of the catheters

This method was satisfactory to the authors in one case It is sound in principle and should be used more often

Ureteroileostomy If the bladder or sigmoid colon cannot be used as a reservoir, transplantation of the ureters to an isolated segment of ileum with one end exteriorized is desirable This is particularly true if the patient's life expectancy is long, as in benign or low-grade malignant disease

The authors' technique follows that of Cordonnier and of Bricker A segment of the distal ileum, 16 to 20 cm in length, is isolated Ileal continuity is re established The proximal end of the isolated loop is closed The ureters are isolated, mobilized as little as possible and divided obliquely, and spatulated The bowel is brought to the ureters, and an end-to-side, mucosa-to mucosa anastomosis is made bilaterally Interrupted 000 or 0000 chromic catgut is used A second layer reinforces the union (fig 5) Inlying rubber ureteral catheters are helpful, but are difficult to maintain in place during the operation

The open end of the loop is brought out an incision in the right abdomen at the waist line Elliptical portions of the skin and fascia are excised to avoid stenosis of the bowel The mucosa of the bowel is fixed to the skin with interrupted 000 chromic catgut Within the abdomen, the ileal segment is further stitched at its exit from the peritoneum The ileal bladder and its mesentery are also fixed to the lateral peritoneum to avoid possible internal hernia

Ureteroileostomy has worked well for the authors in 3 patients One patient had bilateral re-implantation because of hydronephrosis This was thought to be due to overzeal in making a watertight anastomosis

Ureterosigmoidostomy (authors' technique) Ureterosigmoidostomy is indicated when the bladder is lost as a reservoir It is ideal in supplying continence, but it has the disadvantage of producing acidosis, ascending infection, uremia, and hydronephrosis in a larger percentage The authors' methods have been listed The combined intubated mucosa-to mucosa tunneled anastomosis has proven the best The authors' technique follows

The ureters are identified as they cross the iliac vessels They are mobilized below this point and divided The sigmoid is mobilized and sites are selected suitable for anastomosis without tension The left ureter may be brought under the mesentery of the sigmoid if desirable

A longitudinal incision 5 cm long is made in a taenia The mucosa is exposed throughout and opened distally The ureter is placed in this trough, is amputated obliquely at the proper point and spatulated An 8 F Bardam ureteral catheter is passed up the ureter to the renal pelvis This catheter has been fenestrated and the tip amputated (fig 7 A) The distal end of the ureteral catheter is placed within an 18 or 20 F Robinson urethral catheter The urethral catheter is passed into the colon and down to the rectum where it is removed by an assistant (fig 7 *B*) The contained ureteral catheter is sutured to the perineal skin (fig 8) During intubation of the second ureter the surgeon holds the first indwelling catheter while the second is being withdrawn through the rectum

The full thickness of the ureter is sutured to the mucosa of the colon with interrupted 000 or 0000 chromic catgut sutures The ureter is buried in the trough with interrupted or running sutures through the muscularis and serosa of the colon (fig 6) Epiploic appendages further reinforce the suture line The colon is fixed laterally and the anastomosis may or may not be extraperitonealized as is convenient The ureteral catheters and a rectal tube are left in place seven to ten days

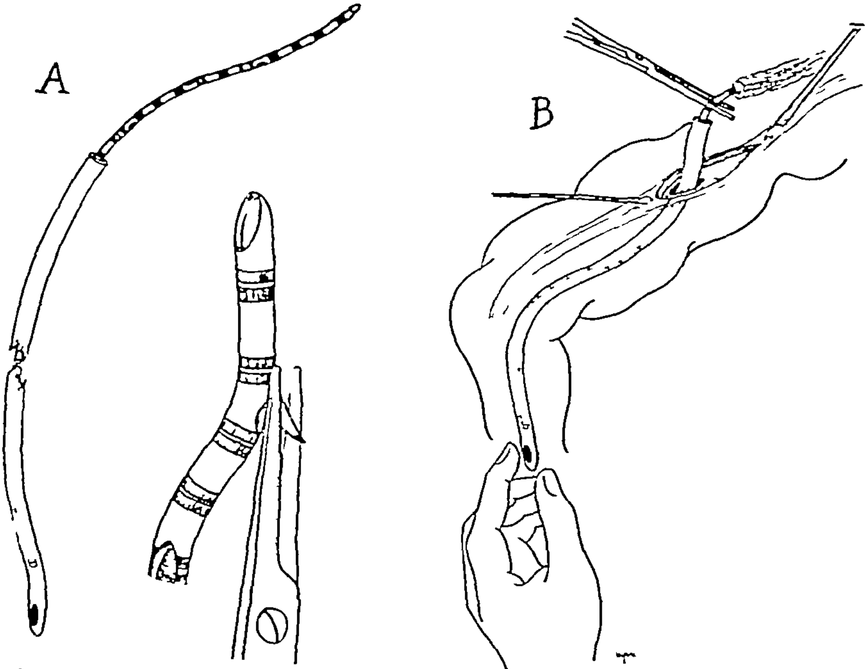

FIG 7 A preparation of ureteral catheter and placement within urethral catheter *B* passage of urethral catheter through rectum

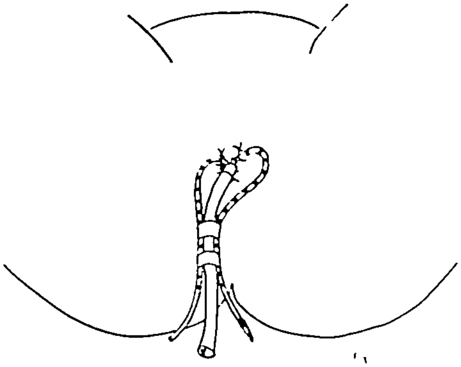

FIG 8 Fixation of ureteral and rectal catheters to perineum Left ureteral catheter cut obliquely

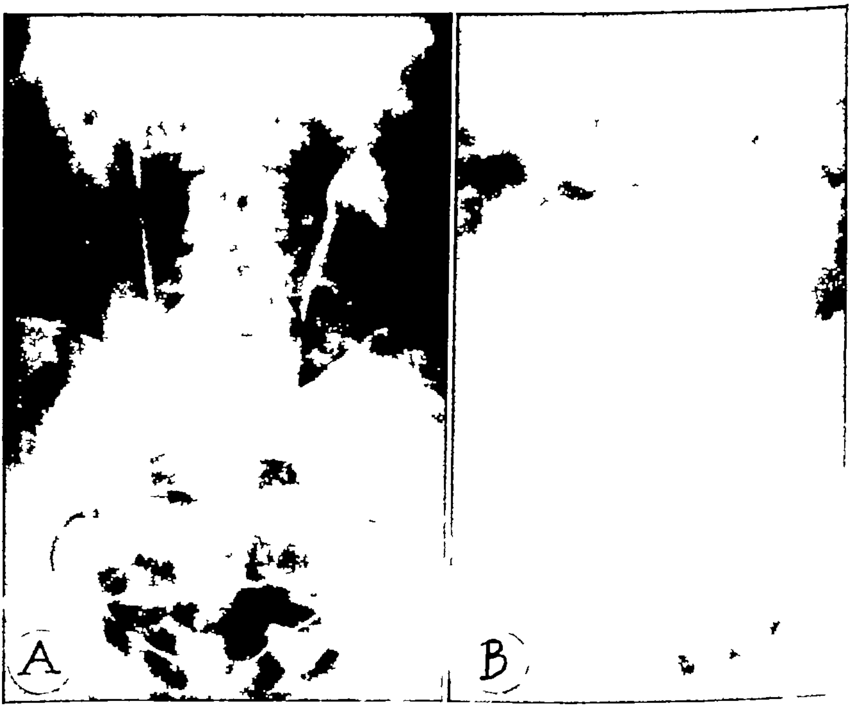

FIG 9 Pre and postoperative pyelograms of patient who underwent ureterosigmoidostomy by authors' method

This method has proven satisfactory and much better than the other methods (fig 9) The indwelling catheters insure a good urinary output, a smooth postoperative course, splint the anastomosis, allow injection of radiopaque fluid, differential function studies, and urinalysis, if desirable The authors' accurate method of intubation eliminates the previous uncertainty of placing ureteral catheters and extracting them from the colon

Cutaneous ureterostomy Cutaneous ureterostomy is indicated in 1) loss of the bladder reservoir, as in tuberculosis, 2) failure of ureterosigmoidostomy, 3) to temporarily divert urine from a destroyed kidney before later nephrectomy, and 4) to direct the urine from an obstructed solitary kidney

The technique employed includes careful retroperitoneal dissection to preserve blood supply and to avoid redundancy or kinking The ureter is approached through a muscle splitting incision and is brought out through a stab incision at belt line level Two methods of anastomosis have been used The first includes interrupted suture of the full thickness of the spatulated ureter to the skin, the second production of a mucosal rosette through redundancy of the ureter outside the skin surface

The operation is safe It is especially adaptable to solitary kidneys if no other reservoir is feasible

DISCUSSION

From the patient's viewpoint, any ideal method of ureteral implantation should preserve continence, continuity, and avoid external devices The physician wishes these advantages as well, but primarily should aim to create a physiologic arrangement to conserve renal substance avoid obstruction reflux, infection and reabsorption No one method meets all of these requirements

Ureterosigmoidostomy fulfills the patient's wishes, but the other qualities may be lacking Restoration of continuity by the standard methods of ureteroneocystostomy and ureteroureteral anastomosis, or by the new and future methods as cystoureteroplasty and ureteroileocystoplasty is excellent, if the bladder is present In its absence, if ureterosigmoidostomy to the intact bowel is rejected, continence must be sacrificed to gain renal physiologic balance One can attain continence of urine with the rectal bladder, but fecal incontinence follows through the coincident colostomy The intrasphincteric perineal colostomy and rectal bladder may solve the problem, but the authors think this possibility is unlikely

At present, the authors feel that ureteroileostomy is the safest though not the most convenient procedure to use for patients with benign disease who have lost the bladder reservoir On the other hand, so many do well after the combined Coffey 2 ureterosigmoidostomy, it may be advisable to use this procedure first In case of failure, ureteroileostomy may be instituted at any time Since 91 4 per cent of patients subjected to ureterocolostomy by the combined Coffey 2 technique gain acceptable results, the chance of a possible future secondary operation may be justified Certainly ureterocolostomy is the most desirable method of diversion for those with malignant disease The present status of the authors' patients with ureterocolostomy for benign disease done by the combined Coffey 2 technique encourages continued recommendation of this procedure despite present poor longevity figures

SUMMARY

The authors' clinical impressions have been presented The record compares with the experiences of others The best methods have been recommended and described The authors' modification of the combined Coffey 2 mucosa-to-mucosa ureterocolostomy is recommended as the best method

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USE OF Y-PLASTY FOR OBSTRUCTION OF VESICAL NECK

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No single treatment for contracture of the vesical neck and of median bar in children or adults has been consistently successful The use of Young's cold punch was the earliest method It proved inadequate due to the inability to remove sufficient tissue and the dangers of perforation involved in the use of a blind instrument The transvesical approach to the bladder neck with the removal of a wedge of posterior neck tissue was then introduced Results from this method are often inadequate because of difficulties in visualizing the bladder neck and inability to remove sufficient obstructing tissue It is also likely that many of the failures are due to prompt recurrence of the contracture or median bar

With the advent of the modern resectoscope, transurethral electroresection became popular for treating this condition in children and adults The disadvantages are numerous In children, the infant resectoscope affords poor visualization for adequate resection and for the control of bleeding Additional dangers are possible urinary extravasation and fistula formation The rate of recurrence of contracture and median bar following endoscopic resection is high in both children and adults

Following the widespread use of the retropubic approach it was soon adapted for the correction of bladder neck contracture in children It consisted of a vertical incision in the anterior prostatic capsule which is extended for a short distance into the anterior bladder wall This exposed the condition at the neck to full view so that it could be adequately resected The incision was then closed vertically in the same manner as it was opened (fig 1, *A*) Thirty-two such cases have been reported,[1-4] and an additional 6 cases by our service [5] The reported results postoperatively were good, but long term followup reports are lacking Two of our patients, both operated on at the age of 4 years, had obstructive

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Appreciation is expressed to Dr George R Horton, director of Urology, Division I, Kings County Hospital, Brooklyn, N Y for invaluable aid and encouragment

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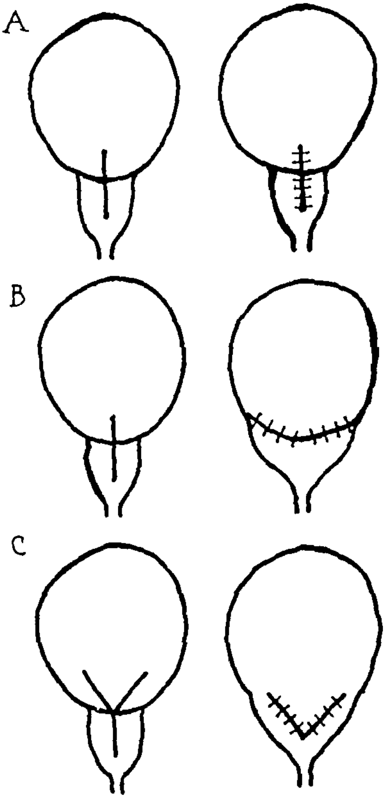

FIG 1 A vertical incision with vertical closure *B*, vertical incision with transverse closure *C*, Y plasty Y incision with V closure

difficulties 3 years later due to significant recurrences of bladder neck contracture We expect to report the long term condition of all 6 patients in the near future It may well be that even adequate open excision may not be the final answer since obstructive scar can recur despite extensive removal

In 1953, Dr Bradford Young[6] suggested a possible solution He used the retropubic approach and opened the anterior prostatic capsule and bladder vertically as before After resection of the bladder neck obstruction, however, he closed the incision transversely (fig 1, *B*) This procedure serves to enlarge the neck, so that if some scar did recur the neck would presumably remain adequate This may also be done in the female by incising a short distance into the anterior urethra Drs Nesbit and Crenshaw[7] suggest that another beneficial factor with this type of closure is that normal bladder tissue is brought into an area of scar and thus depresses future scar formation They have used this method in eight children and fourteen adults with vesical neck obstruction with favorable results

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TABLE 1 *Summary of clinical findings*

Patient	Status	Previous Treatment	Symptoms	Residual Urine (cc)	Cystoscopic Findings	Bladder Capacity	Microscopic Urinalysis
1 J S male age 41 yrs # 20296	Preoperative	Sounds	Severe frequent urination dysuria nocturia 5×	75	Severe bladder neck contracture mild cystitis	Normal	Many W B C /high power field
	Postoperative 11 months		No frequency no dysuria nocturia 0–1×	4	Bladder neck of adequate caliber	Normal	8 W B C/HPF
2 C H male age 46 yrs # 44670	Preoperative	T U R and sounds	Severe frequent urination nocturia 3×	20	Median bar mild cystitis	850 (cc)	2 W B C/HPF
	Postoperative 7 months		Minimal frequency no nocturia	0	Bladder neck of adequate caliber	700 (cc)	No cells
3 F E male age 48 yrs # 48797	Preoperative	None	Severe frequent urination nocturia 6× Complete retention	400	Severe median bar bladder diverticulum mild cystitis	Normal	Many W B C/HPF
	Postoperative 6 months		No frequency nocturia 0–1×	30	Bladder neck of adequate caliber	Normal	0-1 W B C/HPF
4 R S male age 34 yrs # 59186	Preoperative	Sounds	Severe frequent urination nocturia 4–10× cloudy urine	25	Contracture of bladder neck moderate cystitis	150 (cc)	8 W B C/HPF
	Postoperative 4 months		No frequency nocturia 1×	0	Bladder neck of adequate caliber	350 (cc)	2 W B C/HPF
5 H A male age 48 yrs # 56798	Preoperative	None	Frequent urination nocturia 3× mild dysuria	140	Contracture of bladder neck moderate cystitis	Normal	15 W B C/HPF 2 R B C/HPF
	Postoperative 4 months		No frequency no dysuria nocturia 0–1×	0	Bladder neck of adequate caliber	Normal	5 W B C/HPF
6 J W male age 54 yrs # 4228	Preoperative	Sounds	Frequent urination nocturia 5×	60	Severe median bar	Normal	No cells
	Postoperative 1 month		No frequency no nocturia	0	Bladder neck of adequate caliber	Normal	0 1 W B C/HPF

In 1954, Drs Bradford Young and Goebel[8] reported the cases of 7 children done by this method with good results In addition they employed a modification of the transverse closure, which is the Y-plasty, in two children with excellent results

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[8] Young, B W and Goebel, J L Retropubic wedge excision in congenital vesical neck obstruction Stanford Med Bull 12 106–123, 1954

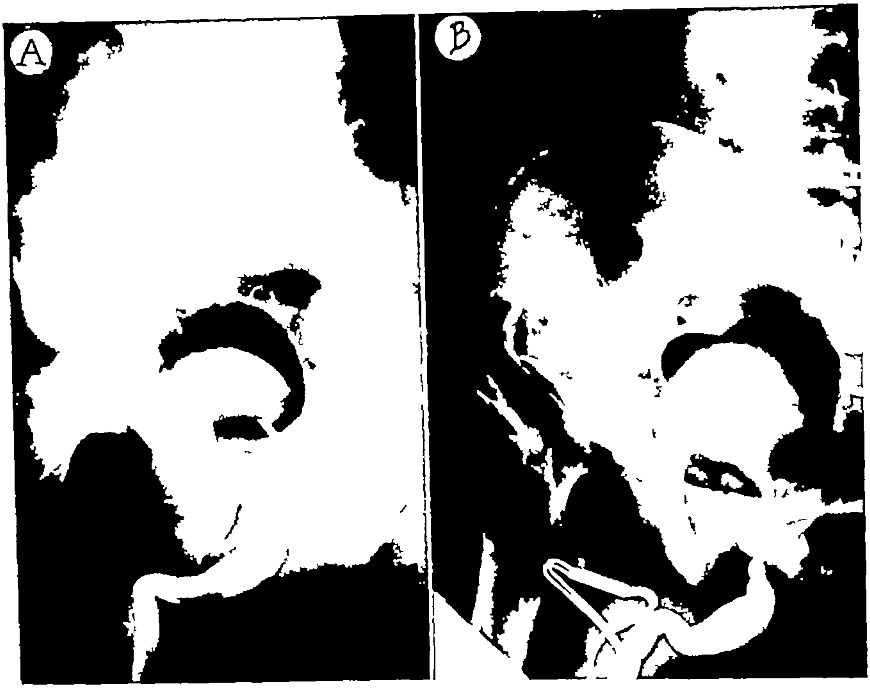

FIG 2 Case 2 C H, 46 year-old male with median bar Patient underwent transurethral resection of median bar 9 months prior to preoperative urethrogram Oblique views of cystourethrograms *A*, preoperative, *B*, postoperative

Drs Flocks, Prendergast, Marberger, and Culp[9] [10] have also reported the Y-plasty operation in two adults with excellent results

The Y-plasty operation is begun by approaching the anterior prostatic capsule and the lower bladder in the usual retropubic manner It is necessary to determine the exact position of the bladder neck before the complete Y-incision can be properly made Such orientation is difficult unless the junction of the prostatic capsule and bladder is first opened Therefore, a short vertical incision long enough to insert a finger is made at the approximate site of the vesical neck in the midline The exact location of the neck can then be determined by palpation The incision is continued with the vertical limb of the Y extending inferiorly through the anterior prostatic capsule, being careful to avoid injury to the external urethral sphincter In the female, the vertical limb of the Y is made by a short incision from the bladder neck into the proximal anterior urethra The lateral limbs of the Y are then made from the bladder neck cranially into the anterior bladder wall for approximately three centimeters The lateral limbs form an angle of approximately 75 degrees The bladder neck contracture or median bar can then be excised under excellent vision In closing the incision, the apex of the triangle of bladder wall thus freed is brought inferiorly to the distal point of the vertical limb of the Y The opposing edges of the prostatic capsule and bladder wall are sutured and thus a large V is formed from the original Y incision (fig 1, *C*) The result of widening the neck and bringing normal bladder

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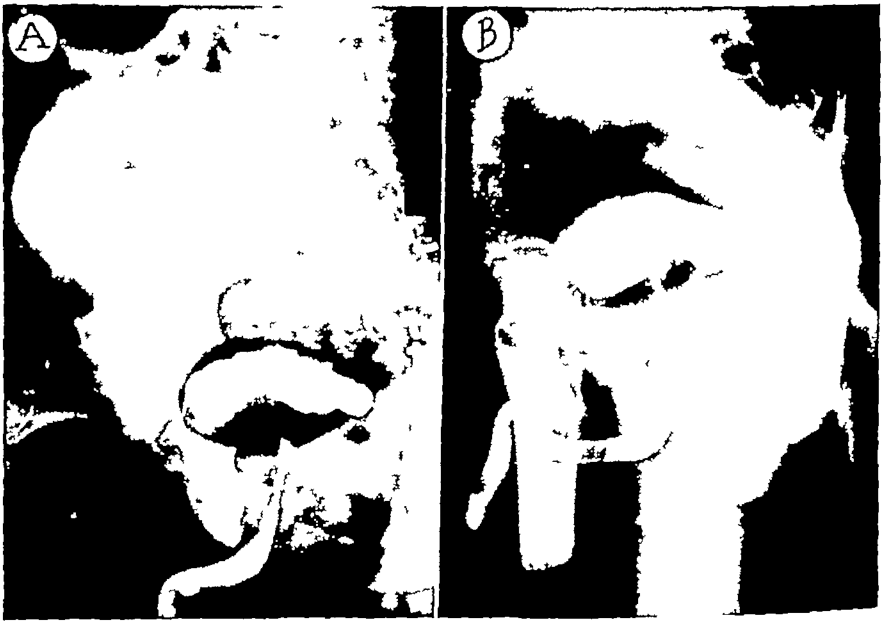

FIG 3 Case 3 F E, 48-year old male with severe median bar and vesical diverticulum Oblique views of cystourethrograms *A*, preoperative, *B*, postoperative

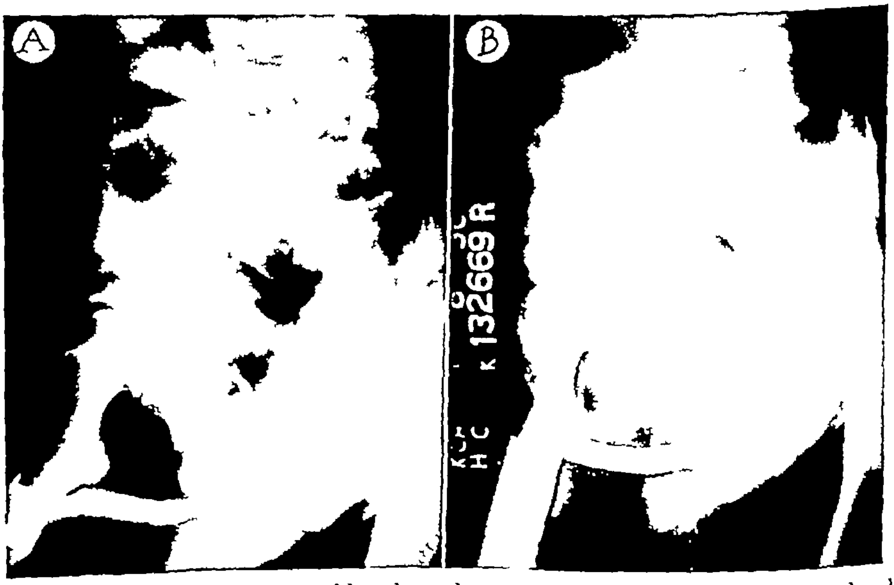

FIG 4 Case 4 R S, 34 year old male with contracture of vesical neck Note also diverticulum like structure of proximal urethra which did not apparently contribute to preoperative symptoms as shown by lack of symptoms following Y plasty for neck contracture of cystourethrograms *A* preoperative *B* postoperative

tissue into a scar area is achieved The Y incision and V closure are essentially not very different than the transverse closure but since the prostatic capsule is practically immobile it appears that the Y incision can be closed more easily and with less tension and distortion than the transverse closure Drs Bradford Young and Goebel have stated that a Y incision is technically easier to close than the transverse closure of a longitudinal incision

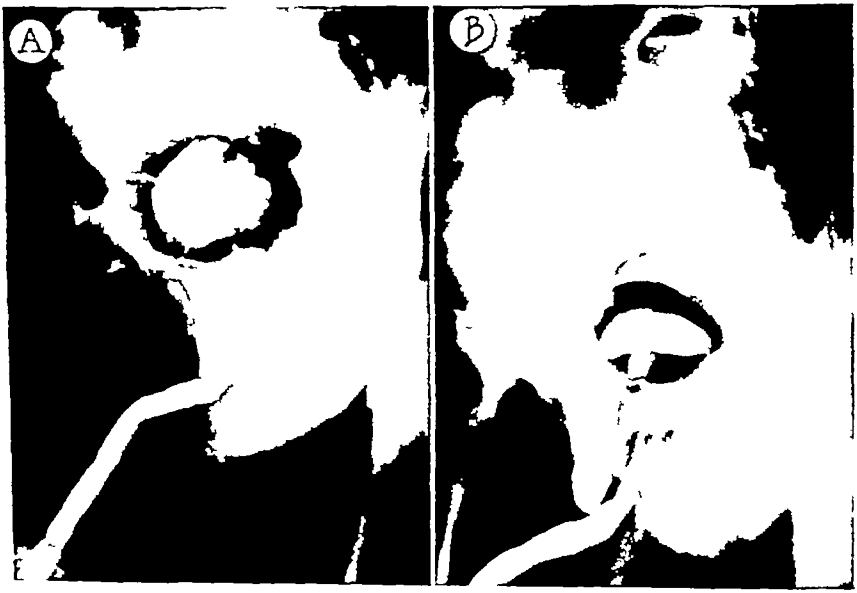

FIG 5 Case 5 H A 48 year-old male with contracture of bladder neck Oblique views of cystourethrograms A preoperative B postoperative

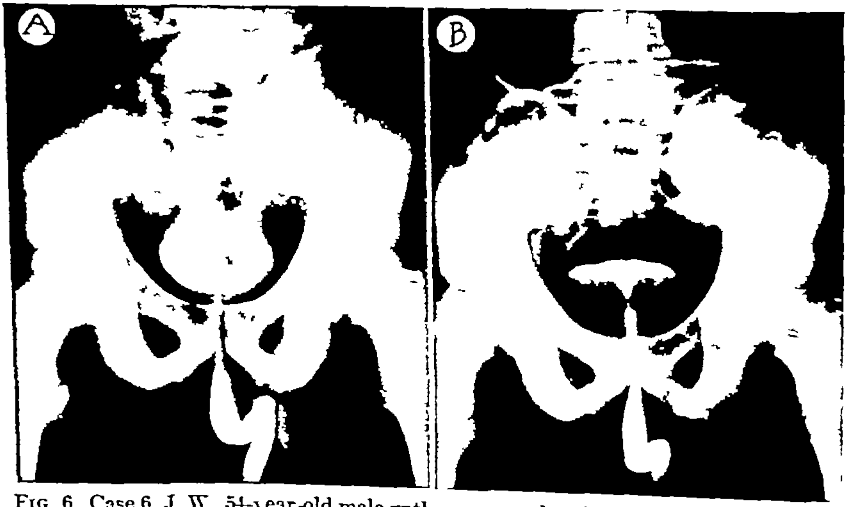

FIG 6 Case 6 J W 54-year-old male with severe median bar Anterior posterior views of cystourethrograms A preoperative B postoperative

Since May 1955, we have performed the Y plasty operation for contracture of the bladder neck or median bar in 6 adults In each patient, the contracture or bar was resected after the Y incision was made and the V closure was done, as already described The upper urinary tract was normal in each patient before and after operation In table 1, the preoperative and postoperative symptoms and objective findings of each case are reported Preoperative and postoperative cysto-aero-urethrograms of 5 patients are shown in figures 2 to 6 Cystourethrograms of our first patient are unfortunately unavailable Note the wide funnel shaped postoperative vesical neck in contrast to the preoperative decreased caliber of the vesical neck in each patient

DISCUSSION

As shown in table 1, one patient had a transurethral resection of a median bar 9 months prior to operation, sounds had been passed on others for varying periods with only temporary partial improvement Symptoms and cystoscopic evidence of contracture or median bar together with trabeculations of the bladder indicated obstructive uropathy in all of our patients Several had a significant residual urine and one patient had complete retention

The operation is not technically difficult and does not require any unusual instruments A 22F or 24F many-eyed catheter was used to drain the bladder by way of the urethra Cystostomy drainage was not used in any patient A ¼ inch Penrose drain was left to drain the space of Retzius Bleeding through the urethral catheter was minimal in all except one patient whose urine at first cleared but moderate bleeding began the eighth postoperative day and continued for 2 days, after which the patient recovered uneventfully Although there was usually slight seropurulent drainage suprapubically via the Penrose drain for several days, there was no suprapubic drainage of urine in any patient Our experience indicates that the suprapubic Penrose drain can be removed on the seventh day and the urethral catheter on the eleventh day

These 6 patients have been followed for only one to eleven months so that any results are far from conclusive To the present time, however, we are very satisfied Symptomatically and objectively improvement has been remarkable in all In no case has there been any urinary incontinence or any effect on sexual potency

CONCLUSIONS

Previous methods used in the treatment for contracture of the vesical neck and of median bar in children and adults are frequently unsatisfactory Early results in 6 adult patients using retropubic excision of bladder neck contracture or median bar with Y-plasty reconstruction of the vesical neck are very satisfying, but only additional cases and long term followup studies will determine if such improvement is permanent

ADDENDUM

Since writing this paper, three patients have had semen analysis in the postoperative period Two have normal ejaculation and all normal findings One patient (C H) had had a previous transurethral electroresection of the vesical neck (see above) following which his semen volume was decreased to ½ cc This has not been altered by the Y-plasty operation although his sperm count is 50 million/cc

Fourteen patients have now undergone the Y-plasty operation with continued satisfactory results

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EXCRETORY CYSTOMETRY: A MORE PHYSIOLOGIC METHOD

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Cystometry and its relationship to diagnosis and treatment of bladder dysfunction is not new (Adler, Rose, Schwarz). It is not the purpose of this paper to relate the pros or cons of cystometry. However, one cannot agree with the statement that, "at present we consider cystometry superfluous for practical purposes." (Brendler, and others). Suffice it to say that it is another adjunct or aid toward the diagnosis and treatment of bladder dysfunction.

Recent textbooks discuss the method of making a urological diagnosis from cystometrograms, yet, they fail to instruct the reader on the importance of doing logically, first a neurological examination of the patient. Abnormal neurological findings should be the first suggestion of a neurogenic bladder. Sufficient stress has not been given generally to the fact that conditions other than neurogenic bladder, i.e., cystitis, vesical calculi, prostatic enlargement, vesical neck contracture, and other obstructions can simulate neurogenic findings on cystometry.

This writer has been impressed, for a long time, by the following discrepancy. Patients with residual urine of from 500–1,000 cc or more, when tested on the wards, would on cystometry show hypertonicity of the detrusor with a capacity of only 75 to 150 cc and low residuals.

Realizing that the retrograde method of cystometry is not physiological, the more recent textbooks were reviewed in that respect. None mentioned this fact. Yet, classification, diagnosis and treatment have been offered on this basis of findings which are collected with a non-physiologic method.

Adler has performed "decremental" cystometry, starting with a full bladder. A catheter was introduced and responses were recorded cystometrically as each decrement was released from the bladder. Schwarz has stated that "in the normal bladder the reading is almost the same with physiologic and artificial fill but under pathological conditions (hypertonicity of detrusor) the difference is remarkable."

At this paraplegia center it has been recognized for some time that cystometry is non-physiologic. Munro was conscious of this fact when he stated that increments of 25 to 50 cc of fluid are "physiologically fantastic" whereas continuous flow is more physiologic. He performed cystometry at 100 drops per minute.

The purpose of this paper is 1) to introduce "excretory cystometry" and 2) to compare the various results obtained with five modified methods of cystometry, namely, a) regular retrograde cystometry with a whistle tip catheter, b) regular retrograde cystometry with a Foley bag catheter, c) retrograde cystometry with an increment of 100 drops per minute and a whistle tip catheter, d) excretory cystometry with a whistle tip catheter, and e) excretory cystometry with a Foley bag catheter.

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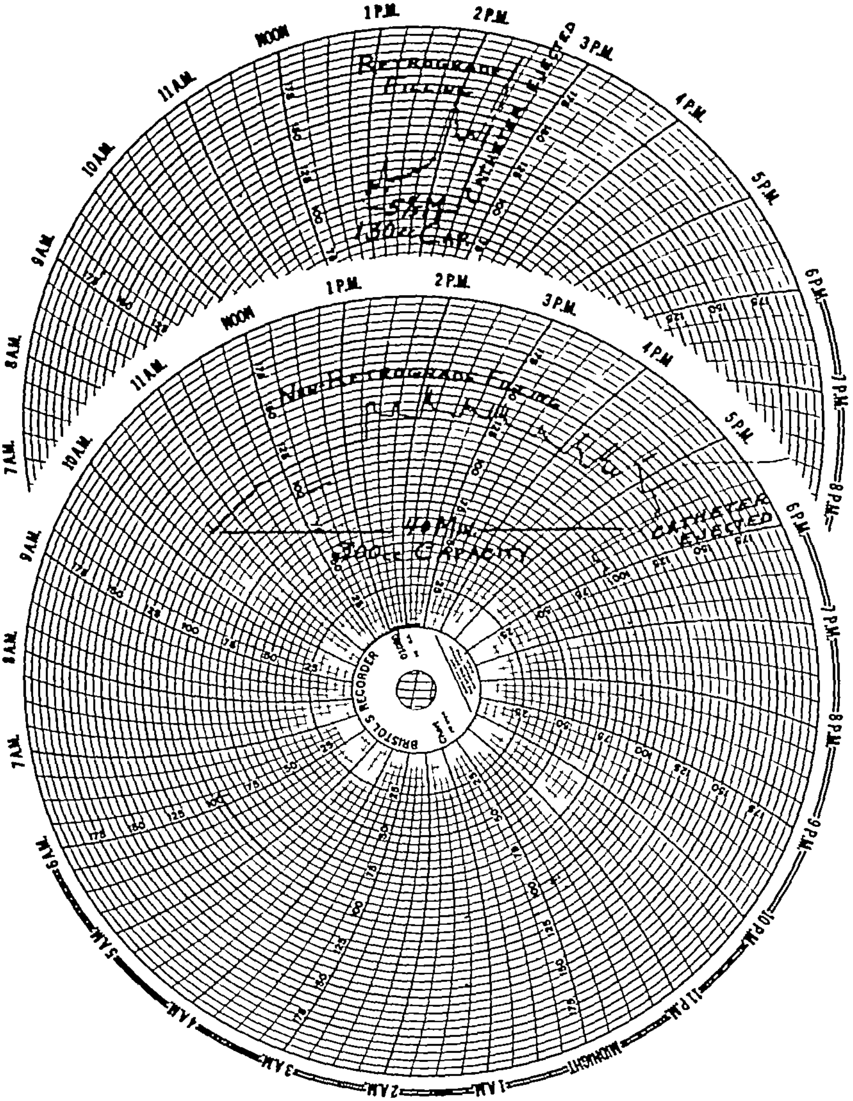

Fig 1 Retrograde and excretory cystometry performed on same patient with upper motor neuron lesion of bladder Milam Leberman cystometer used Note that capacity with excretory method was more than double that of retrograde method

MATERIAL AND METHODS

Thirty patients were studied Three patients were "catheter free" prior to the testing, two had lower motor neuron lesions and one an upper motor neuron lesion Four patients became "catheter free" during or shortly after the studies, of which two were discharged before completing the testing All four had upper motor neuron lesions

One hundred and forty-five cystometric tests were studied

Fifteen of the 30 patients had cervical lesions of which ten were complete and five incomplete cord lesions All had an upper motor neuron type of neurogenic bladder

Four of the 30 patients had complete lesions from T-1 to T-6 with upper motor neuron neurogenic bladders

Six of the 30 patients had complete lesions from T-7 to T-12 Four had an upper motor neuron whereas two had a lower motor neuron type of bladder

Five of the 30 patients had lumbar cord lesions of which three were complete (1 upper and 2 mixed types of bladders) and two had incomplete lesions (1 upper and 1 lower motor neuron type)

There were, therefore, 25 patients with an upper motor neuron type of bladder, three with a lower motor neuron, and two with mixed types

Twenty-eight of the 30 patients sustained a spinal cord injury One patient had a progressing cord syndrome 6 months prior to laminectomy with no subsequent improvement and an undetermined etiology despite a biopsy of a small amount of tissue Another patient had sequelae of a viral transverse myelitis, he had a bilateral pudendal neurectomy and transurethral prostatic resection prior to these tests, but his bladder function remained imbalanced

The time interval since injury or onset of disease and the performance of these tests ranged from four to sixty-seven months

The five tests were performed within a 2-week period on each patient However, only one test per individual patient was performed on a single day in order to avoid possible bladder stimulation from previous testing The increment for the retrograde methods, a, b, c, was distilled water at room temperature

The technique of performing cystometry was as follows

a) Regular retrograde cystometry with a No 20 whistle tip catheter was performed after the bladder had been emptied The Y tube was attached to the catheter, from one limb of the Y tube the tubing led to the Lewis cystometer Through the other limb of the Y tube fluid entered in a continuous flow at the rate of 25 cc per minute This instillation was terminated either by a detrusor contraction which ejected the catheter, or it was discontinued at a volume of 400 cc (This method is the routine at our Paraplegia Center)

b) Regular retrograde cystometry with a Foley bag catheter was performed similarly to that with a whistle tip catheter The 5 cc Foley bag was inflated after the bladder was emptied When a voiding contraction of the detrusor was noted the bag was released in order to permit ejection of the catheter Four hundred cubic centimeters were the limit of volume if the catheter was not expelled

c) Cystometry with a whistle tip catheter and an increment of 100 drops per minute was performed in the same manner as regular retrograde cystometry with a whistle tip catheter

d) "Excretory cystometry" with a whistle tip catheter was performed as follows The patient drank hourly one glass of water from 6 00 a m until the scheduled time for cystometry The fluid intake was continued during cystom etry A No 20 whistle tip catheter was gently introduced into the urethra and the bladder was emptied Strain, crède, or any other method was not used to empty the bladder since this might set off reflex activity The tip of the catheter must be in the bladder, it was then connected to the Lewis cystometer in the usual manner The intravesical volume was supplied by the patient's excreted urine Sufficient time was allowed for stabilization before the investigation was started in order to avoid the recording of responses caused by such stimuli as change of catheters moving the patient to the testing room, transferring the patient from the gurney to cystoscopy table, and the like (The procedure should be preferably done at the bedside) Cystometry was continued until the catheter was ejected, but it was terminated after 1½ to 2 hours, if the catheter was not ejected in order to prevent possible overdistention

e) Excretory cystometry" with a Foley bag catheter was performed similarly The time limit was the same, namely 1½ to 2 hours, if a voiding contraction detrusor appeared on the graph, the Foley bag was deflated and the catheter was permitted to be ejected A No 20 Foley bag (5 cc) catheter was used

In order to assess the volume-time ratio for excretory cystometry, i e the amount of urine produced within 1½ to 2 hours the patient underwent preliminary testing on the ward over a period of two to three days in the following manner The patient drank a glass of water (240 cc) hourly from 6 00 a m until bedtime The amount of urine at the end of each 1½ hour period was recorded Experience showed that despite the regular and equal input, the output remained inconstant Therefore, excretory cystometry was done at a time when high peaks were anticipated, based upon such preceding studies Otherwise, cystometry may require 2½ hours or more in order to reach the true capacity of the viscus This method of testing can be simplified by simply measuring the output, which accumulates in the bottle at 1½ hour intervals, this obviates clamping the catheter off The occasional difference of urinary output of the individual patient, measured at set times on different days, ranged up to a maximum of 990 cc (in a 1½ hour period) and was entirely unpredictable An additional intake of extra fluid did not materially alter the output Differences of output occurred in the presence of essentially normal renal function as assessed by excretory urograms

A very satisfactory method of performing excretory cystometry can be done with the Milam-Leberman cystometer It is especially suited for excretory cystometry because it permits recording over many hours on the same chart (fig 1)

RESULTS

The capacity of the bladder was studied with the five different methods 400 cc was taken as normal

Twenty-five patients with upper motor neuron bladders showed the following

Regular cystometry with a whistle tip catheter 14 patients had capacities below normal, 11 had capacities above normal

Regular cystometry with a Foley bag catheter 13 patients had capacities below normal, 11 had capacities above normal One patient is excluded because he did not undergo this examination

"One hundred drops per minute cystometry" with a whistle tip catheter 12 patients had capacities below normal, 10 had capacities above normal Three patients are excluded because they did not undergo this examination Excretory cystometry with a whistle tip catheter 5 patients had capacities below normal, 20 had capacities above normal

Excretory cystometry with a Foley bag catheter 3 patients had capacities below normal, 21 had capacities above normal One patient is excluded because he did not undergo this examination

The capacities of 3 patients with lower motor neuron lesions were above normal with each of the five types of cystometry, and the same was true for two patients with mixed lesions

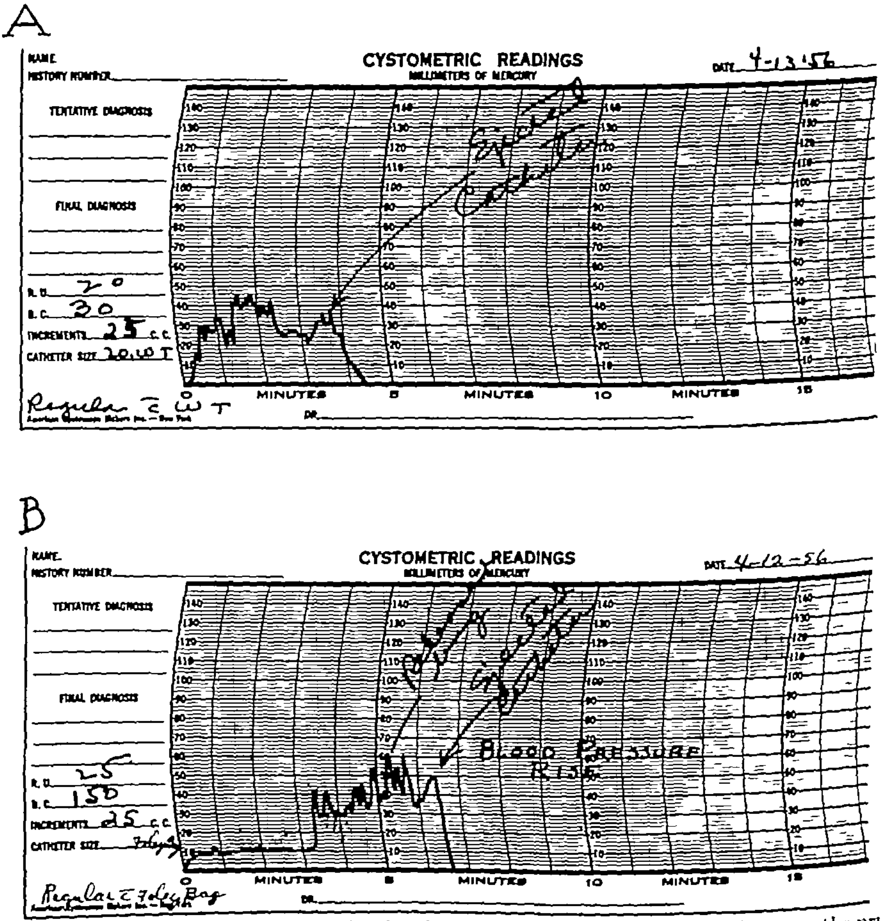

Fig 2 *A*, regular cystometry with whistle tip catheter Patient injured 11 months prior to examination (cervical 7 clinically complete) Catheter ejected in 4 minutes Capacity 30 cc *B*, regular cystometry with Foley bag inflated Same patient as A Catheter ejected after 6½ minutes with symptoms of pathologic autonomic paroxysmal hypertension Capacity 150 cc

When the ability of the detrusor to eject the catheter (voiding contraction) was studied, 25 patients with upper motor neuron lesions showed the following

Method a Twelve patients ejected the catheter who had capacities below normal and 1 patient who had a capacity above normal

Method b Twelve patients ejected the catheter who had capacities below normal, and none with a capacity above normal

Method c Eleven patients ejected the catheter who had capacities below normal and 1 patient who had a capacity above normal

Method d Four patients ejected the catheter who had capacities below normal, and 3 patients who had capacities above normal

Method e Three patients ejected the catheter who had capacities below normal and 2 patients who had capacities above normal

None of the patients with lower or mixed motor neuron bladders ejected the catheter with any of the five methods

The capacities did not markedly differ with any of the three methods of retrograde cystometry (a b, c) The number of patients who showed capacities above normal was essentially the same with both excretory methods (d, e)

The ability to eject the catheter was almost the same among patients subjected to the three retrograde methods (a, b, c) Essentially the same was true for the patients subjected to the two excretory methods (d, e)

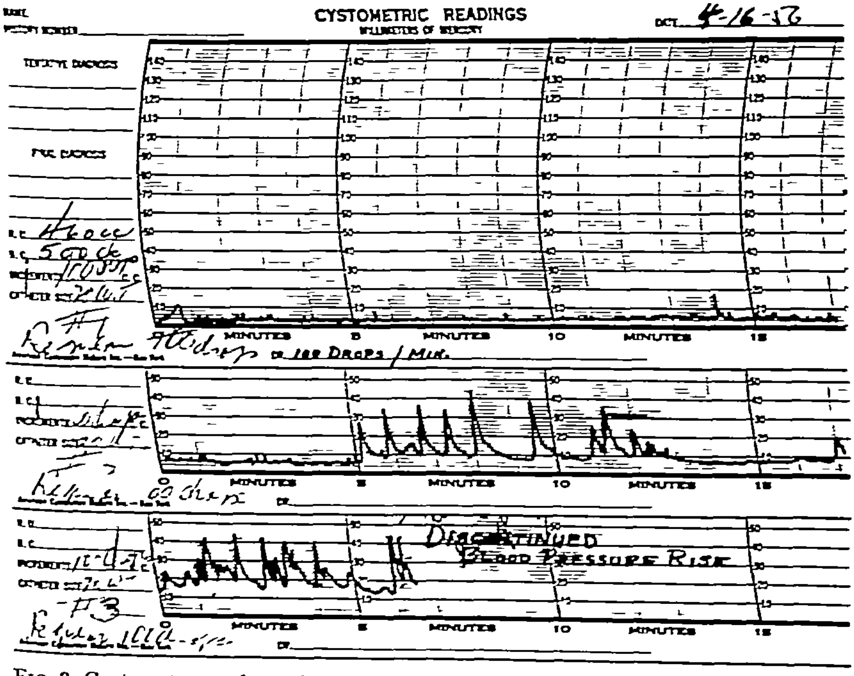

FIG 3 Cystometry performed at 100 drops per minute with whistle tip catheter Same patient as figure 2 Procedure stopped because of paroxysmal hypertension Capacity 500 cc

During or following this study, 4 patients with upper motor neuron bladders developed balanced reflex function All of them ejected the catheter at one time or other during any of the five cystometric examinations The 6 patients who showed hypercapacity with all methods and no ejection of the catheter are still not catheter free One of the patients with a lower motor neuron lesion is still not catheter free, while the other two patients with lower motor neuron lesions were "catheter free" before the study The two patients with mixed motor neuron lesions are still not "catheter free"

The residual urine was not a prominent factor in these studies since these bladders with three exceptions were imbalanced when the studies were started However, the three retrograde methods tended to mislead by showing seemingly a better bladder function than the excretory methods among the patients with upper motor neuron lesions The excretory methods reflected correctly the imbalanced function of the bladder when it was tested by measuring the residual at

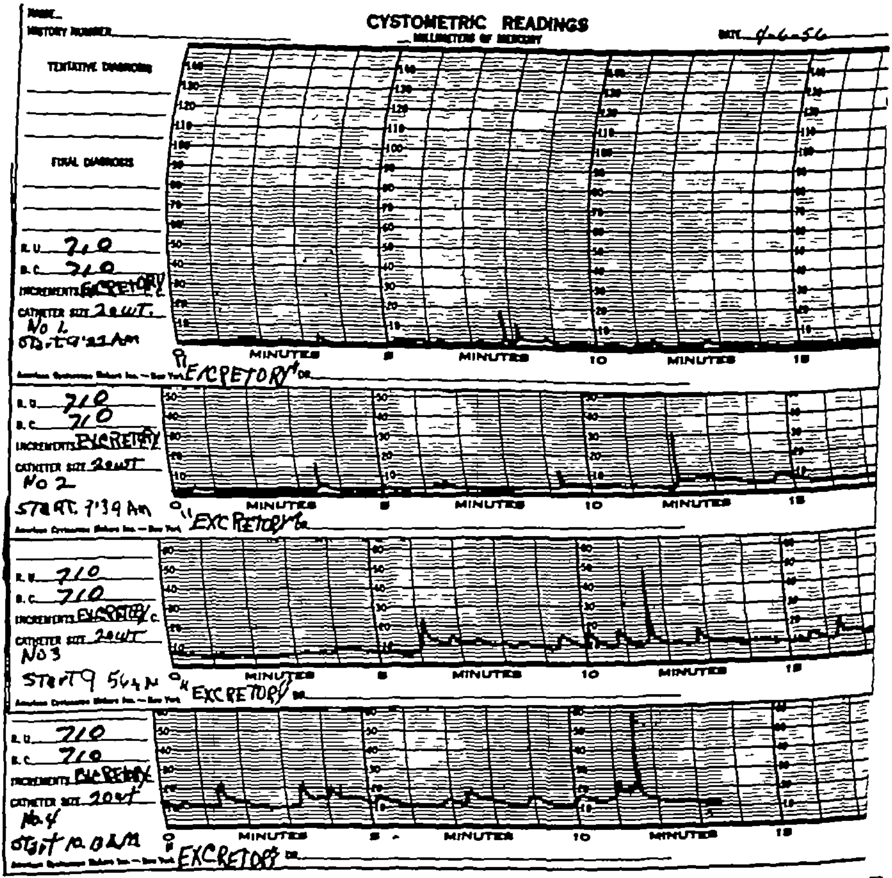

FIG 4 Excretory cystometry with whistle tip catheter Same patient as figure 2 Examination stopped because of paroxysmal hypertension Capacity 710 cc

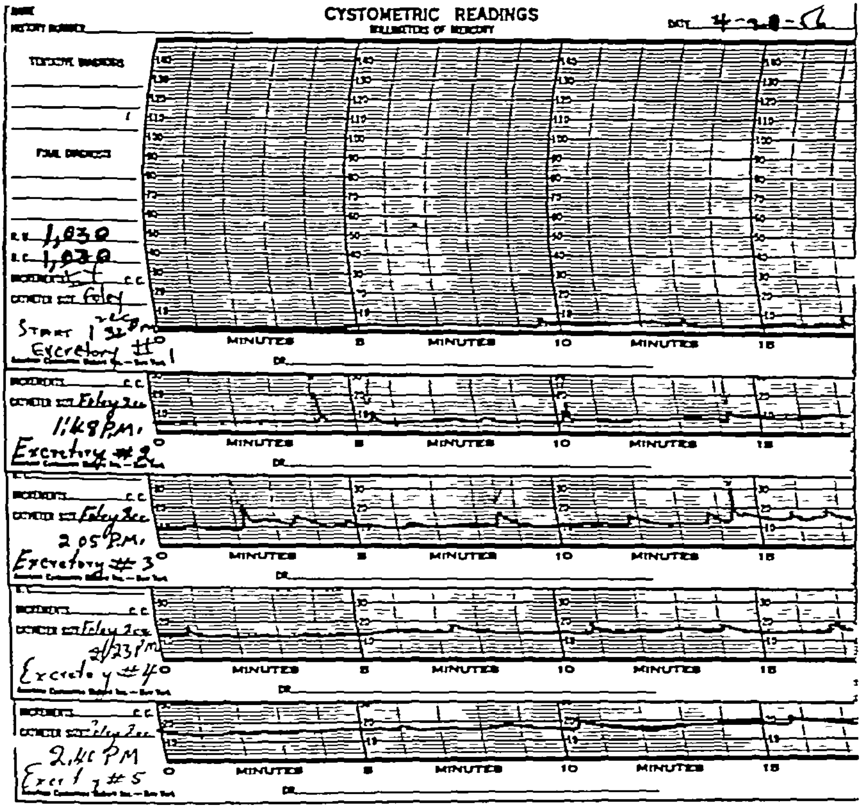

FIG 5 Excretory cystometry with Foley bag inflated Same patient as figure 2 Test stopped because of paroxysmal hypertension Capacity 1030 cc

the bedside The patient with a lower motor neuron lesion and bladder imbalance showed voiding with all methods by using extrinsic pressure One of the two patients with mixed lesions showed no voiding with any one method The other patient with a mixed lesion voided by strain with each method, however, he had had a previous T U R

The base line, indicating detrusor tone, was higher as a whole with the three retrograde methods (a, b c) than with the excretory methods (d, e) among the patients with upper motor neuron lesions (figs 2–5) The base line was essentially the same among the patients with lower motor neuron lesions for all methods The patients with mixed lesions showed a higher base line with the retrograde methods than with the excretory methods

Generally, it was observed that in patients with cervical lesions, the retrograde methods of cystometry (a, b, c) elicited a hypertensive blood pressure response at lower volumes than the excretory method (d, e) (fig 6)

Completeness or incompleteness of the spinal cord lesion did not seem to play a role in this series of cases

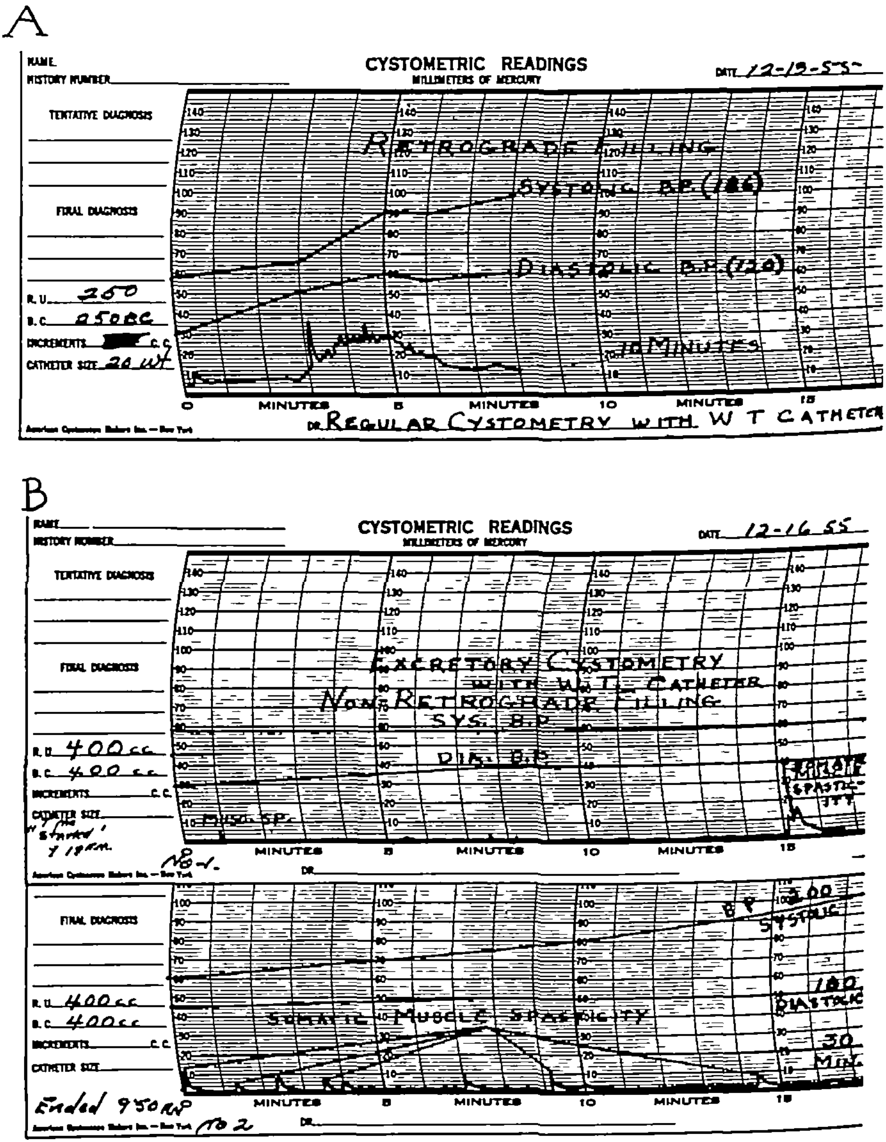

FIG 6 A, regular cystometry with whistle tip catheter Patient injured 19 months prior to examination (cervical 5 and 6, clinically incomplete) Test discontinued because of hypertension Capacity 250 cc *B*, excretory cystometry with whistle tip catheter Same patient as figure 2 Capacity 400 cc

DISCUSSION

In comparing retrograde (a, b, c) with excretory (d, e) methods of cystometry there is a marked difference apparent in regard to capacity The majority of patients with upper motor neuron lesions show subnormal capacities with the retrograde than with the excretory methods This appears quite understandable because the retrogradely instilled volume acts as a more powerful and quick stroke of the reflex hammer (Nesbit), in eliciting the bladder jerk (Bors) than does the gradual and more physiologic increment of the excreted urine However, method c, with an increment of 100 drops per minute (Munro), is closer, but not close enough, to the more physiologic increment of the excreted urinary volume This marked difference is absent, as was to be expected, in patients with lower motor neuron lesion Therefore, truer capacity values will be disclosed with the excretory, rather than with the retrograde methods This in itself is of importance for the management, and also will make it unnecessary to test bladder capacities under spinal anesthesia

Although truer capacities can be obtained with excretory than with retrograde methods in patients with upper motor neuron lesions the true capacity, unimpeded by the stimulus of the indwelling catheter, can be determined only at the bedside Then capacity versus residual urine is tested per time unit Usually this should not exceed one hour since large volumes of urine (more than 500 cc) can be easily excreted during that time If by chance the volume found after one hour is below normal, it should not be mistaken for the true capacity Other factors may be responsible for this shortcoming, such as inadequate fluid intake prior to examination any degree of dehydration following an alcoholic debauchery, or increased spasticity, and the like

Compatible findings are seen in regard to the ability of the detrusor to eject the catheter This again happens in a majority of cases with upper motor neuron lesions with retrograde rather than with the excretory methods This ability to eject the catheter is absent in the majority of lower motor neuron lesions, which is in line with the type of this bladder

Similar observations were made in regard to detrusor tone which tended to be higher (baseline of curve) in a majority of the patients with upper motor neuron lesions on retrograde than excretory cystometry Inasmuch as tone and contraction are properties of the detrusor the parallelism between baseline level and catheter ejection is not surprising

The practical value of the evaluation of these methods applies to the prognosis of future function the prescribing of drugs and eventually the indication for tidal drainage and bladder training

If patients with upper motor neuron lesions tend to eject the catheter with any of the five methods future establishment of useful reflex activity may be expected This must not imply that reflex function will become adequate without some auxiliary procedure If retrograde methods indicate detrusor response but excretory methods fail to do so the future function of such a bladder remains dubious It should not mislead the observer to believe that a strong and even emptying response with retrograde, but not excretory, cystometry will necessarily meet successfully the crucial test which consists of determining the residual urine at the bedside in the given time of one hour If all five methods show higher than normal capacities and no detrusor response the prognosis for future reflex function of the viscus should be guarded In order not to miss the trend of cystometric results both methods should be applied at regular intervals in the same vein, as it has always been recommended for the orthodox method of cystometry

How easy one could mismanage by prescribing a detrusor relaxant drug on the basis of exclusive retrograde cystometry, can be detected only when the excretory or bedside residual methods disclose a condition diametrically opposed to that encountered with retrograde cystometry. Had one followed exclusively the results of retrograde cystometry in this series, 19 of the 25 patients with upper motor neuron lesions would have deserved a trial with a relaxant drug. Actually, none of them needed or received this therapy, because of excretory cystometric results and bedside residual tests.

By the same token the opposite of relaxation, namely stimulation of the detrusor with tidal drainage, must not be indiscriminately based upon the retrograde cystometric results, even if the "100 drops per minute method" is used. The outgoing limb of the tidal apparatus should be adjusted to a height indicated by the values of excretory rather than retrograde cystometry, if overdistention, the foe of all bladder rehabilitation, is to be averted. A similar trend of thought applies to bladder-training. Here, however, it is the ratio of the volume/time unit which is important (Comarr), overdistention may easily occur, if the time is prematurely extended to 1½, 2 or even 3 hours (Munro), based again exclusively upon the bladder response to retrograde cystometry. In such cases the results of excretory cystometry should rather be heeded, which may show far above normal volumes to occur within one hour.

From a practical point of view it is suggested that whistle tip catheters be used for both methods because they don't carry with them the additional stimulus of the bulb on the vesical neck.

SUMMARY

"Excretory cystometry" using the patient's urine as increment is introduced.

The results of regular retrograde cystometry are compared with those of the excretory method using whistle tip and Foley bag catheters, the different effects on capacity, detrusor tone and contraction are reported on 30 patients with each respective method.

The value of excretory cystometry with respect to prognosis of future function, medication, and indications for tidal drainage or bladder training is discussed.

ADDENDUM

Regular (retrograde) cystometry was performed upon patients converted from upper motor neuron bladders to lower motor neuron bladders, 3 patients permanently by subarachnoid alcohol blocks and 3 patients temporarily by spinal anesthesia. Interestingly, with excretory cystometry upon all the 6 patients the capacity was much greater than with retrograde cystometry, even though the reflex activity of the conus medullaris or its fibers was not present.

This phenomenon may possibly explain why over the years we have observed a number of times that following subarachnoid alcohol blocks, a number of weeks *later, the somatic musculature remains flaccid, yet* the bladder empties by detrusor activity.

This would then indicate that since the conus activity (reflex activity) is not present, the mechanism must probably be within the bladder itself.

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PRIMARY OSTEOGENIC SARCOMA OF THE BLADDER

MYRON H NOURSE

In June 1956 Mr C H W, age 44 years, was seen in our office complaining of extreme terminal burning on urination and voiding every hour Catheterization revealed no residual urine The urine was infected A 24F sound was passed easily but "crepitus" was felt

He was admitted to the hospital for further investigation, assuming that a bladder stone was present and the cause of his complaints Excretory urograms showed mild left pyelectasis and ureterectasis The right kidney was normal Cystoscopic examination revealed a huge tumor originating from the posterior wall and dome of the bladder well away from the trigone It measured at least 6 cm in diameter It was bulky and appeared nodular on the surface The base was broad No calculi were present Bimanual rectal examination elicited a mass as large as a small orange which was freely movable A cystogram showed a large filling defect of the bladder An open segmental resection was advised because of the location of the tumor and the lack of demonstrable fixation locally There was no evidence of distant metastasis The chest film was normal Barium enema was normal Films of all long bones and skull were negative for primary or metastatic bone lesion

The patient's past history is important In 1949 a surgical procedure was performed elsewhere on the right kidney, presumably for an aberrant vessel A transurethral prostatic resection for a contracted bladder neck was done elsewhere in 1953 He was first seen by us in June 1955 because of repeated episodes of urinary infection, burning, frequency and nocturia Residual urine was 1 ounce Exploration of the urethra disclosed that a No 22 sound passed with difficulty at the vesical orifice

The patient was admitted to the hospital Excretory urography was normal except for mild left pyelectasis Cystoscopic examination disclosed no abnormalities except a severely contracted vesical orifice A transurethral resection performed June 24, 1955 removed 6 gm tissue Microscopic sections were benign His symptoms were considerably improved and urine became negative

He was not seen again until February 1956 His symptoms had returned and a No 16 catheter was again found to be very tight at the vesical neck The patient was readmitted to the hospital Cystoscopic examination under anesthesia showed a severely contracted bladder neck through which a panendoscope would not pass The resectoscope was then used to enter the bladder with the aid of the cutting loop The remaining scar tissue was widely resected No stone or tumor was seen within the bladder He was discharged 6 days later

The patient was followed in the office at 2 and 3-week intervals He was never completely without symptoms of some type of bladder discomfort He was finally readmitted June 1956 Other significant past history included a healed peptic ulcer of 5 years and histoplasmosis in 1940

Read at annual meeting, North Central Section of American Urological Association, Cleveland, Ohio, October 3-5, 1956

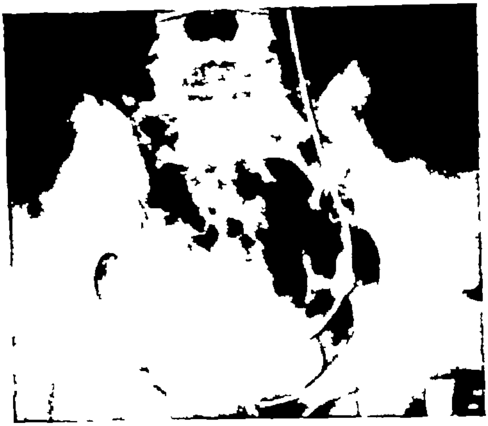

Fig 1 Cystogram showing filling defect of dome and left side of bladder

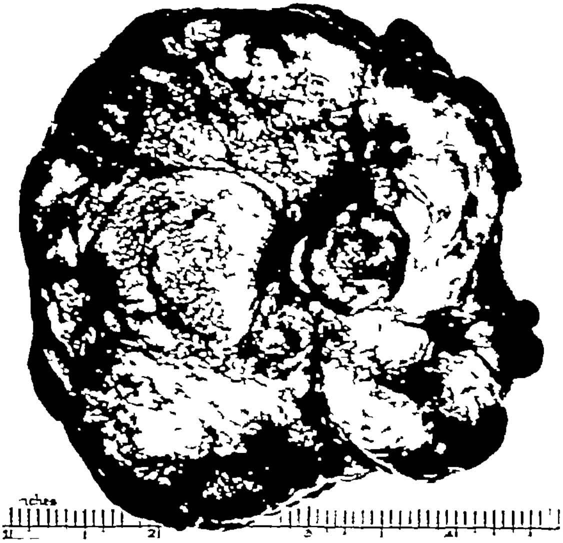

Fig 2 Gross specimen of removed tumor by segmental resection Note normal bladder mucosa around edges Uneven nodular surface appearance is apparent

Physically the patient, a white man aged 44 was of slight build and weighed normally about 100 pounds No particular abnormalities were noted Rectal examination revealed a prostate that was normal in size shape and consistency Blood pressure was 125 75

On July 6 a suprapubic segmental resection of the bladder tumor was accomplished The tumor was not adherent to the surrounding tissue It occupied the posterior wall and dome of the bladder requiring removal of approximately two-thirds of the wall of the bladder No evidence of local metastasis or lymph nodes was found

The gross specimen measured 8 by 8 by 6 cm The surface was nodular and very hard Cut sections showed large depositions of calcium salts Microscopic

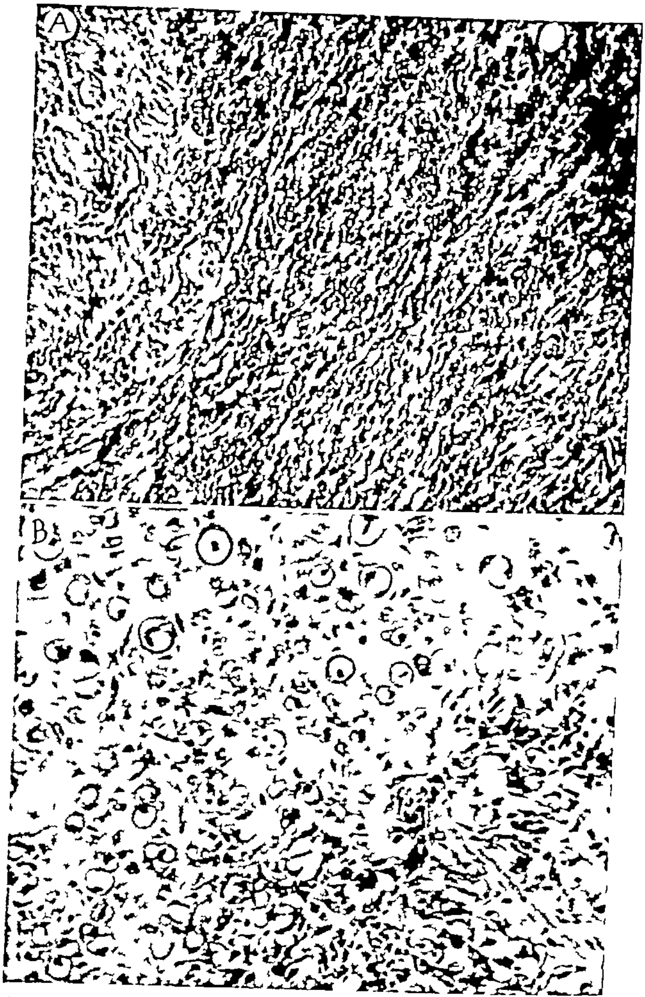

Fig 3 *A*, section of tumor through highly anaplastic portion showing patterns of sarcoma with muscle wall invasion *B*, bulk of tumor shows patterns which go from precartilaginous through definite large islands of cartilage formation to bone All but bone formation is noted in *A*

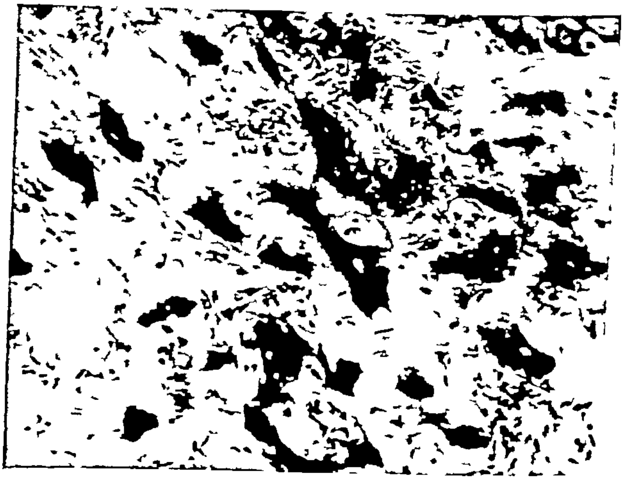

Fig 4 Bone is produced generally by ossification of cartilaginous area Deposits of calcium and bone formation are demonstrated here Cartilage and osteoid are of abnormal variety, as seen in sarcomas Bulk of tumor composed of cartilage and bone

sections showed a highly anaplastic type sarcoma with predominantly cartilage and osteoid tissue

The patient did well for the first 3 postoperative weeks except for a persistent suprapubic fistula An attempt to close it failed Cystoscopic examination 1 month postoperatively was negative for recurrent tumor During the fifth postoperative week he complained of considerable distress in the lower abdomen A large mass that developed in the suprapubic area extended to the umbilicus and filled the pelvis to its lateral borders The mass was hard and fixed Symptoms of partial bowel obstruction soon were noted with finally complete obstruction requiring intubation His downhill course was rapid and he died August 24, 1956, 49 days following surgery An autopsy was not granted

DISCUSSION

Crane and Tremblay in 1943 in an excellent review of all sarcomas of the bladder up to that time were able to find only five that were primary bone producing tumors from their collection of 151 reported cases They added 1 case of primary osteogenic sarcoma of the bladder An interesting observation noted was that of these 6 osteogenic tumors of the bladder, the case of Crane and Tremblay was the only one reported in the American literature, the others being found in foreign journals There has been none reported since 1943 I would like to add our case which makes 7

Hamer and Wishard in 1948 presented a case of a primary osteogenic sarcoma of the kidney in a 76-year-old man This was the second to be reported They mention that a number of extraskeletal ossifying tumors are discussed in the literature Wilson found by careful review 30 cases of bone-forming malignant tumors in soft parts, the histological picture in most of them being compatible with true osteogenic sarcoma This group included thyroid, nipple, gallbladder, chest wall, breast, abdominal wall, kidney, bladder, thigh and calf of leg The fibrous capsule of the kidney has also been known to undergo ossification

The origin of such tumors rests with conjecture rather than fact Metaplasia of bladder mucosa is mentioned Another suggests that the tumors are derived from embryologic rests of the wolffian body, from which the trigone of the bladder develops The transfer of osteoblasts by the bloodstream to unusual locations has been considered A reasonable theory is that fibrous tissue, cartilage and bone are all end products of a common mesoblastic stem Therefore, under certain conditions they may revert or dedifferentiate into an embryonic state and when this occurs fibroblasts may become osteoblasts and form true bone (Leriche and Policard)

It is unfortunate that alkaline phosphatase levels were not obtained on our patient This information might have been of some value for future reports Crane and Tremblay's case was thoroughly studied from this respect including histochemical determinations of the gross tumor This must be done however, before the tissue is fixed

The prognosis is uniformly fatal The tumors grow rapidly and infiltrate locally The majority die in less than 6 months The treatment, in view of the past reports as well as our own, is symptomatic Radical surgery is not the answer Osteogenic sarcoma is well known to be radioresistant so that x-ray and radium offer nothing except discomfort

SUMMARY

A case of primary osteogenic sarcoma of the urinary bladder is presented The patient was a 44-year-old white man who died 49 days after segmental bladder resection X-rays of all long bones and skull failed to disclose a primary site other than bladder

A review of medical literature divulged one other such tumor reported in this country, 5 in foreign periodicals, ours being the seventh

It is certain the tumor developed within a 4-month period because it was not present in February when cystoscopic examination was performed and was present in June at the time of his hospital admission

Prognosis has been uniformly rapidly fatal in usually less than 6 months Treatment at the present time obviously appears to be symptomatic

Surgery or x-radiation is not the answer

I am indebted to Dr Edwin E Pontius, pathologist at the Methodist Hospital because of his keen interest, co-operation and careful preparation of the tissue for microscopic study The detailed, excellent photography has been accomplished by Mr McKinley A Leapley, also of the Methodist Hospital

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* References to pertinent foreign literature are contained in the citations listed Therefore, they will not be repeated

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USE OF ANSOLYSEN FOR URINARY RETENTION

HAZEN L. MILLER

Occasionally, the urologist is confronted with an inexplicable case of urinary retention. Sometimes the patient has been in other hands for a protracted period with either intermittent or indwelling catheter drainage. When much time has elapsed without response to cholinergic drugs or psychiatric persuasion and with still no end of the impasse in sight, we are only too glad to consider one more resource short of surgery.

The patient was a 22-year-old male college student with an asthenic diathesis and tranquil behaviour. Before my first visit to his home on November 29, 1955, he had had no urinary or neurological disturbance except for difficulty in initiating micturition after a prolonged automobile ride. It may also be significant that he had been under the care of a proctologist for a few days because of a perianal paraesthesia. When seen by me at 9 p.m. he had not passed urine all day but had no discomfort except a sensation of weight. He was relieved of about 1200 ml. of urine by catheter, and asked to go to the hospital in the morning for an x-ray for a possible calculus. When seen 12 hours later, he had not voided and his bladder was palpably distended. A large quantity of urine again drained forcelessly. The patient was then admitted to the hospital and was studied with the help of a neurologist and neurosurgeon. The only findings of note were hyperactive deep tendon reflexes, weakness of dorsiflexion and deviation of the right foot on heel and toe walking, hyperesthesia to pin prick in the right crural and right plantar regions and absence of abdominal reflexes. Myelograms and spinal fluid findings were normal. Cystometrograms indicated slight atony with appreciation of filling at 200 to 250 ml. and a strong desire to void at 350 to 400 ml. Cystoscopy showed only questionable fine shallow trabeculation of bladder.

The patient was maintained on intermittent filling and emptying of his bladder by a Foley bag catheter, intermittent bladder irrigations, and also urecholine 10 mg. t.i.d. and mild urinary antisepsis. On December 8 the catheter was removed and he was given an opportunity to urinate but failed absolutely. On December 9 the catheter was replaced and irrigations resumed. On December 12 a neurosurgeon, Dr. F. R. Latimer, as locum tenens for the consulting neurosurgeon, suggested the use of ansolysen which he had observed to have apparently induced micturition as a side effect in 2 cases of hypertension. Therefore, the drug was given (20 mg. q.i.d. for 3 days) in place of the contemplated formidable procedure of unroofing the sacrum to look for an involved nerve. When the catheter was removed after the patient had taken ansolysen for 3 days, he promptly urinated and has had no difficulty since. The blood pressure dropped from 136/84 to 120/70.

Read at annual meeting, North Central Section of American Urological Association, Cleveland, Ohio, October 3-5, 1956.

It is interesting to note that concomitant constipation was also immediately and entirely relieved

I have since used ansolysen in three other cases in which the only common feature was persistent retention of urine In all three early termination of the retention resulted

Brief abstracts of these cases follow

M S, a woman aged 55, postoperative pelvic repair, retention up to 1150 ml without definite desire to void In spite of prolonged use of urecholine retention had persisted 1 month before ansolysen was started In two or three days thereafter she was voiding competently and soon afterward left the hospital able to empty her bladder The highest blood pressure reading before treatment was 220/106, the lowest afterward 120/70

V H, a man aged 47, post-traumatic, injury to left shoulder and cervical spine He was unable to void and a catheter had been inserted 3 days before I saw the patient Ansolysen 20 mg t i d for 3 days Catheter was removed and patient was able to urinate readily from then on Highest blood pressure recording before treatment was 120/80, the lowest afterward was 118/60

E G, a woman aged 79, nine days post-traumatic, fracture of left femur with insertion of Smith Peterson nail Retention of urine with overflow incontinence and difficulty in controlling defecation Bladder palpable half way to umbilicus but not tender and no desire to void, when seen by me on August 4, 1956 Ansolysen 10 mg q i d for 2 days, then 20 mg t i d Three days later, when catheter was inadvertently removed, micturition commenced in a normal manner with no recurrence of chronic retention Blood pressure reading preceding ansolysen, 145/80, after 3 days, 128/70

In addition to the foregoing cases, I wish to report the 2 cases of which Dr Latimer was cognizant and upon the basis of which he recommended ansolysen

A 43-year-old woman had multiple sclerosis, hypertension and chronic urinary retention She was under the care of Dr Andrew Wilson who prescribed ansolysen 20 mg t i d during an episode of complete retention The patient voided 48 hours following treatment and has had no further urinary difficulty

A 60-year-old man had lues Tabes dorsalis was suspected when complete urinary retention followed herniorrhaphy The patient was given ansolysen 10 mg t i d and the following day he voided without difficulty, which has continued

Three other more recent successful cases have been reported to me verbally by the attending neurosurgeon of the patient whose case is the first one reported in this paper

Ansolysen, or pentolinium tartrate is commonly used in cases of hypertension associated with side effects of dizziness, impotence, etc It is also reputed to cause urinary retention Since postural hypotension often occurs, its use in the normotensive patient, especially the elderly one, should be guarded

The medical director of Wyeth Laboratories replied to my letter of inquiry that he was unfamiliar with the effects on micturition reported here

It is my impression that any benefit from the use of ansolysen in retention is due to partial blocking of the sympathetic ganglia that permits relaxation of the involuntary sphincter and thereby puts an atonic detrusor into balance

This unconvincing but highly suggestive series is presented 1) to disseminate knowledge of a rather innocuous drug possibly helpful in a difficult situation and 2) to bring it to the attention of those who may throw light on its effect on vesical function, if any

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ACID PHOSPHATASE ACTIVITY IN BULBOURETHRAL GLANDS

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AND

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Primary carcinoma of Cowper's glands is rare[1, 2, 3] and occasionally difficult to diagnose In several reported cases this tumor was originally considered a prostatic carcinoma Recent experience with another case of possible carcinoma of Cowper's gland brought up the possibility of differentiation from carcinoma of the prostate by histochemical methods

The high concentration of acid phosphatase in prostatic epithelium is well known Alkaline phosphatase activity has been demonstrated in the bulbourethral glands of rats, mice, hamsters, guinea pigs, and rabbits[4, 5] However, no mention of acid phosphatase activity in the bulbourethral glands was found in a review of the literature

This study was undertaken to determine whether there was acid phosphatase activity in the bulbourethral glands Its absence from normal and neoplastic bulbourethral tissue could be utilized to differentiate tissues of bulbourethral origin from those of prostatic

METHOD

The original method of Gomori (1941)[6] with modifications of Goetsch and Reynolds (1951)[7] was used to stain for acid phosphatase activity Four-mm thick blocks of prostatic and bulbourethral tissue were fixed in chilled absolute acetone Further dehydration was accomplished with two changes of absolute acetone at room temperature The tissues were cleared in two changes of benzene, ½ hr each, and then imbedded in paraffin Slides were made of sections 4–8 microns thick and dried in air They were then incubated in buffered $Pb(NO_3)_2$-Na glycerophosphate solution at 38° C from 15 min to 6 hours Incubated slides were then washed in water, dilute acetic acid, and water After immersion in dilute $(NH_4)_2S$, the slides were deparaffined and counterstained with eosin Sites of acid phosphatase stain brown or black

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Incubation solution 30 cc M acetate buffer pH 5 (100 cc 6% NaAc $3H_2O$ +
50 cc 6% HAc)
10 cc 5% Pb $(NO_3)_2$
60 cc H_2O
30 cc 2% Na glycerophosphate
Filtered and diluted 2–3 times with H_2O when used

RESULTS

Brown and black lead sulfide precipitate was present in prostatic and bulbourethral glandular tissue after as short an incubation as 15 minutes With this short incubation, most glandular elements contained stain, but there was great variation in quantity In the bulbourethral glands stain was found in both nucleus and cytoplasm In the prostate some areas showed staining of only nucleus and basement membrane, and in others only the supranuclear cytoplasm and some luminal debris were stained

After 2 hours' incubation, stain was seen in greatest quantity in the supranuclear cytoplasm and in the intraluminal secretion of the prostate The amount of stain in the bulbourethral glands was much less than in the prostate but the glandular elements were nevertheless distinctly stained

There was some variation in staining of some sections, even after several hours' incubation Occasionally histologically normal tissue contained no stain whatsoever With greater periods of staining, prostatic glandular tissue showed up more darkly than the bulbourethral But in addition, endothelial cells, some fibroblasts, and nerve tissue began exhibiting stain

SUMMARY

Both prostate and bulbourethral tissues stain positively for acid phosphatase activity Qualitatively then, this method will not differentiate the two tissues Further improvements in standardization of solutions and technique of acid phosphatase staining could make it possible to differentiate these tissues quantitatively

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MALIGNANCY FOLLOWING MUMPS ATROPHY OF THE TESTICLE

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The literature on this subject is scanty and therefore the report of even one new case seems justified because it is only through larger statistics that we can hope to become more enlightened

A F Weyerbacher reported 2 cases in 1938 The first one involved a man aged 23 who one year prior to the development and operation for a unilateral testicular teratoma had bilateral mumps orchitis The second patient, aged 26, had what is described as mumps orchitis 4 months prior to the development of a "carcinoma of the right testicle " The patient died with pulmonary metastases Some doubt may be voiced in this case on account of the very short interval

Judson P Gilbert on reporting a case in 1944 reviewed the literature and found 24 similar cases in over 5500 detailed records on testicular carcinoma—an incidence of 0 5 per cent This figure has to be compared with a general incidence of mumps orchitis (in 1000 cases collected by Stengel from 27 sources) of 18 2 per cent

The incidence of testicular tumor formation following nonspecific atrophy of the testis (trauma, ectopia and developmental anomalies) is given as 1 5 per cent by Gilbert

The age of the patients ranged from 30 to 37 years The time elapsed between mumps orchitis and tumor development was from 7 to 12½ years

Pathologically they are classified as

Unicellular	13
Teratoid	9
Miscellaneous	2

Gilbert's own case involved a 39-year-old man who had bilateral mumps orchitis prior to the development and removal of his right testicle for "embryonal cell carcinoma with lymphoid stroma "

J S Haines and Henry Grabstald reported two more cases in 1950, the first one a man, aged 51, who had mumps atrophy at the age of 20, the second one a man, aged 31, who had his atrophy at the age of 10 The cause, however, was unknown The diagnosis in both cases was seminoma

Both papers, the one of Gilbert and of Haines and Grabstald, came to the conclusion that testicular tumors are more common after nonspecific atrophy and that there is no connection between mumps orchitis and tumor development

Our patient, R S , age 30, entered the hospital on May 21, 1955 The only pertinent part of his history is an attack of mumps at the age of 12 with a complicating inflammation of his right testicle After it healed, the testicle was much smaller than the left one He has been married 11 years and was the father of

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one healthy child While taking a bath approximately one week prior to admission he discovered his right testicle to be harder and larger than it was before There was definitely no pain and no loss of weight

On admission he gave the appearance of a very healthy man weighing 225 pounds Blood pressure 128/60 Pulse 84 Temperature 37 2 The general physical examination was entirely normal

The left testicle epididymis and cord were normal The right testicle was smaller than the left one, but it was of stony-hard consistence with no irregularities There was a softer mass connected posteriorly with this tumor This could well be the epididymis The cord was normal The tumor was freely movable in the scrotum The prostate gland was normal

Urinalysis ph 4 5 Albumin negative Sugar negative Blood negative Microscopic Rare white blood cell and epithelial cells

Blood count Hemoglobin 14 3 gm Red blood cells 4 6 million White blood cells 10 400 Neutrophile cells 73 per cent Eosinophile cells 1 per cent Basophile cells 1 per cent Lymphocytes 25 per cent

Blood chemistry Blood sugar 123 mg per 100 cc Blood urea nitrogen 12 mg per 100 cc

Sedimentation 15 mm 60 minutes

Frog test Negative

Kline test Negative

X-rays of the chest, skull, the whole length of the spine, pelvis and long bones showed no sign of metastases An excretory urogram was normal and in particular had no deviation of the ureters

The diagnosis was malignancy of the right testicle

Operation (May 23, 1955) General anesthesia with ether and cyclopropane The operation began with an incision in the scrotum The tunica dartos was severed and the tunica vaginalis was carefully lifted, opened and the testicle was evulsed without any pressure Both testicle and epididymis appeared normal in form However the consistency of the proximal portion was extremely hard as compared to the distal portion There was heavy vascularization over the hard portion A Penrose drain was now placed around the cord and used as a tourniquet to prevent spreading of tumor cells An incision was made into the hard portion which showed a homogeneous brown tissue with no interstitial differentiation There was no doubt about the malignant character With the tourniquet kept in place the testicle was wrapped in gauze and the operation completed by removing it with the length of the cord through the inguinal canal The operation was completed by repairing the inguinal canal and placing a thyroid drain into the scrotum

The patient made a good postoperative recovery and was given a total of S300 r through five ports between May 25 and June 18 1955

He is at this date working and well Subsequent x-rays of the chest on July 1 September 7, December 13 and April 16 1956 were normal

Pathological report The gross specimen consists of a testicle moderately enlarged measuring 5 by 3 by 3 cm The spermatic cord is attached to the testicle

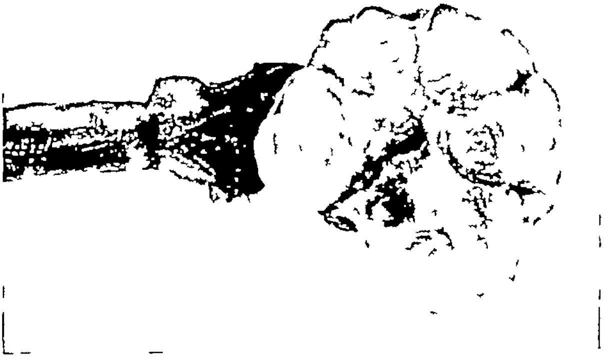

Fig 1 Gross specimen of testicle with tumor

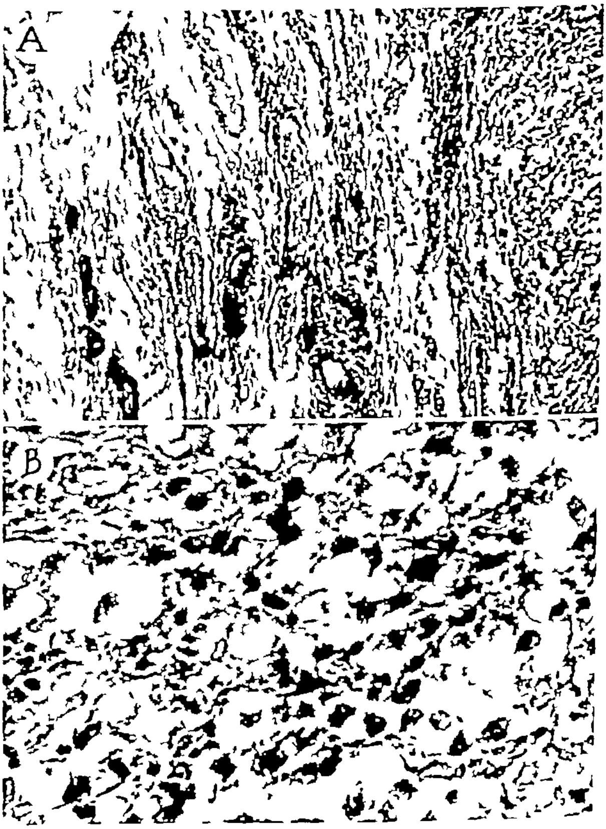

Fig 2 *A*, low power Note atrophic tubules adjacent to tumor tissue *B*, high power Note typical embryonal cell carcinoma

measuring 13 cm in length, 1 to 1½ cm in diameter, and considerably congested with the vessels prominent The epididymis is present in usual position over the surface of the testicle The outer surface of the testicle shows the tunic smooth, bluish gray On section, the testicle is almost completely replaced by tumor with a thin rim of testicular tissue present over the margins of the tumor This tissue surrounding the tumor is grayish brown, fleshy and shows no evidence of tubule formation The tumor itself bulges on section, is coarsely lobulated, somewhat firm, yellowish gray with focal areas of necrosis and hemorrhage grossly recognizable

Microscopic description Testicle Section 1 shows the testicle almost completely replaced by tumor tissue The tumor consists of solid sheaths of large and medium size cells arranged in masses separated by a vascular fibrous stroma In some areas, the stroma is abundant and fibrillated In other areas the stroma is very scant The tumor proper consists of solid and loosely arranged masses of large polyhedral and oval cells showing relatively large nuclei which in many areas almost completely fill the cell spaces The nucleoli are prominent and enlarged A few mitotic figures are noted There are focal areas of necrosis throughout the tumor and in some areas the tumor shows lymphocytic infiltration of the stroma One section shows a small mass of testicular tissue attached to the tumor Here, the tubules are small, atrophic, showing complete absence of spermatogenesis, marked thickening of the basement membranes and small nests of Leydig cells present Diagnosis Embryonal cell carcinoma of the testes " See figures 1 and 2

DISCUSSION

We do not know whether the cases of Weyerbacher are included in Gilbert's statistics There is some doubt as to whether one should include them because of the short interval between the reported mumps and the origin of the tumor Adding Gilbert's case and one of Haines and Grabstald our case would bring the reported number of testicular malignancies following mumps atrophy to twenty-seven

Dr Mostofi in his splendid presentation at the 1956 American Urological Association meeting in Boston included mumps atrophy of a testicle among the conditions favoring tumor development

This is in contrast to the aforementioned opinion of Gilbert, as well as that of Haines and Grabstald In fact, these authors state that testicular tumors are more common after nonspecific atrophy

However, it is obvious that the number of known cases is much too small to permit the drawing of conclusions Publication of further cases should be encouraged

SUMMARY

A case of testicular malignancy (embryonal cell carcinoma) following mumps atrophy is reported bringing the number of known similar cases to twenty-seven

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CYTOLOGY IN CLINICALLY BENIGN CASES OF PROSTATIC HYPERTROPHY

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The importance of cytologic investigation for the diagnosis of malignant degeneration of prostatic tumors, up to now, has been disputed by most authors In recent years, only a few have advocated its advantages Peters and Frank,[1] Gunn and Ayre,[2] Silva-Inzunza,[3] etc

Based on our former investigation of cells in fresh unfixed and unstained material observed under the phase-contrast microscope[4 6] we have searched for malignant cells in cases of prostatic hypertrophy clinically considered as benign We have preferred studying fresh unfixed and unstained material as we are convinced that in this way the observation of cells is done under conditions close to normal Staining qualities are often altered by pH of the urine and by the length of time cells remain in the urine, and morphology is altered by the techniques employed in fixing, especially drying

MATERIAL AND TECHNIQUE

We have looked for abnormal cells in the sediment of freshly voided urine following prostatic massage and in scrapings from cut surfaces of recently removed tumors within two hours after operation Preparations are not fixed or stained When necessary, material has been diluted in normal saline Observation is made with the phase-contrast microscope with from 900–1200 diameters under oil immersion

CELLS

The following changes registered in cells are considered as indications of malignancy

a) *Size* Malignant cells of epithelial origin are usually larger in size than the normal cells of the originating epithelium Some of them may be gigantic

b) *Cytoplasm* Phagocytized material from other cells—cannibalism—or vacuolization may be observed

c) *Nucleus* Changes may affect the size and number of nuclei as well as the nuclear membrane and the size and number of nucleoli The nucleus is enlarged

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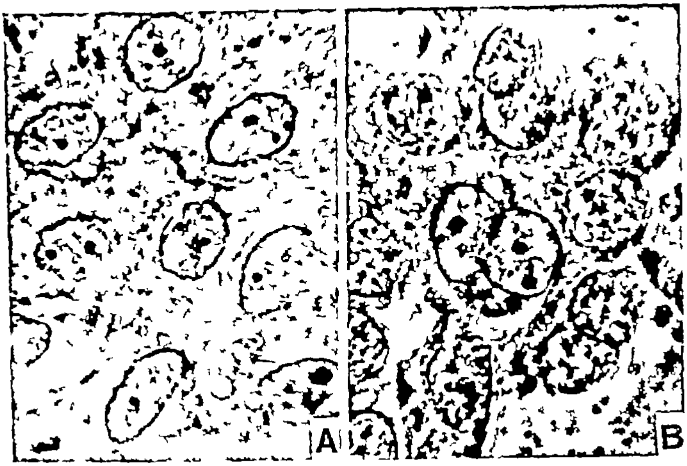

FIG. 1. Fresh unfixed and unstained prostatic material (phase contrast 900 diameters). *A*, exfoliative cells in urine voided immediately after prostatic massage showing partial festooning or corrugation of nuclear membrane and more than one micronucleolus. *B*, malignant cells from surface scraping of a clinically and histopathologically benign prostatic tumor.

and may occupy the greater part of the cell. There is an evident rupture of the nucleo cytoplasmic ratio, less noticeable in small rounded cells. Nuclear enlargement alone is not a definite sign of malignancy. Free nuclei may be mistaken for cells with loss of the nucleo-cytoplasmic ratio but, by throwing the nucleus out of focus, if it is a cell the cytoplasm will appear as a clear surrounding band.

Two or more nuclei, partially fused or separated, may be present in the same cell. As normal cells of certain portions of the lining epithelium of the genitourinary tract may be bi- or multinucleated, the pathological significance of this finding is minimized if unaccompanied by other changes suggestive of malignancy. The nuclear membrane is thickened segmentarily or totally festooned or corrugated. These changes of the nuclear membrane are not observed when nuclei are abnormally enlarged, and we think they represent one of the earliest indications of malignancy. Multiplicity of nucleoli, and especially the presence of macronucleoli are very suggestive of malignancy.

Sex chromatin, a planoconvex, hemispheroid or triangular mass adjacent to the inner surface of the nuclear membrane, when present is easily identifiable and should not be confused with a nucleolus. The proportion of cells with sex chromatin in a count of 200 to 400 vesiculous nuclei can give us along with the cytologic nature of the tumor, an approximate idea of the tumor's sex and possible origin—feminoid (muellerian remnants) or viriloid[7].

Cell abnormalities suggestive of malignancy, described in preceding paragraphs, may be found singly, two or more or all in a single cell. From our observation of malignant cells from other sources we conclude that in prostatic material early cancer changes are also principally found in the nuclear membrane and nucleoli. Occasionally during the early stage of malignancy some cells show

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Coutts W. L. and Silva Inzunza E. Investigacion de cromatina sexual en celulas de tumores malignos o benignos de la prostata. Rev. chilena Urol. 18: 70, 1955.

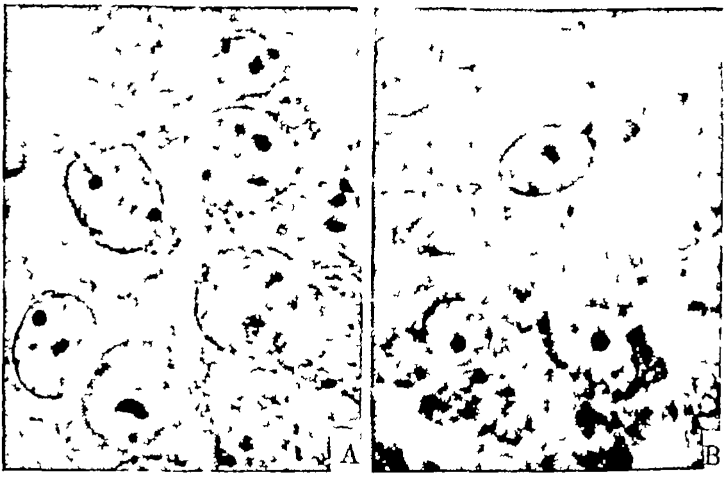

FIG 2 *A*, typical malignant cells from surface scraping of a clinically surgically removed benign prostatic enlargement Anisokariosis, partial corrugation of nuclear membrane, multiplicity of nucleoli (phase contrast 900 diameters) *B*, sex chromatin and nucleolus in a vesiculous nucleus of a normal cell from a cut surface scraping of a surgically removed benign prostatic enlargement (phase contrast 900 diameters)

slight changes of the nuclear membrane and contain several micronucleoli in the karioplasm or show a slight increase in the size of the nucleus which may contain several micro- or macronucleoli

All cancers contain abnormal cells but all abnormal cells do not necessarily derive from a cancer When we find typical cancer cells in urinary sediment and in scrapings from the removed tumor and the pathologist fails to find malignancy, we consider such cases as of surface or "in situ" cancer of the hypertrophied prostate

RESULTS

Our investigation was carried out in 200 cases of clinically benign prostatic hypertrophy All were examined after removal at the Institute for Pathological Anatomy of our Medical School These cases had not previously received any hormonal treatment When the urine contained large numbers of pus cells, search for cancer cells was deferred until infection had subsided If silver nitrate or other antiseptic irrigations were being used they were stopped and a "per os" antibiotic cocktail administered

The 200 cases have been divided into 3 groups A) those in which exfoliated cells in the urine voided immediately after prostatic massage were studied, B) those in which cells in scrapings from cut surfaces of the recently removed tumor were studied and C) those in which both types of cells were studied

Group A includes 123 cases Cytology and histopathology agreed in 92 cases (74 7 per cent), 76 were benign and 16 were malignant In 25 cases (20 3 per cent) cytology was malignant and histopathology benign In 6 cases (4 8 per cent) cytology was benign and the tumor was found malignant by the pathologist

Group B includes 48 cases Tumor pathology and histopathology agreed in 36 cases (75 per cent), 26 were benign and 10 were malignant In 11 cases (22 9 per cent) cytology was malignant and histopathology benign Only in 1 case (2 per cent) was cytology benign and histopathology malignant

Group C includes 29 cases Exfoliative cytology, tumor surface scraping cytology and histopathology all agreed in 24 cases (82 7 per cent), 18 were benign and 6 malignant Among the remaining 5 cases results were variable in 2, both exfoliative cytology and histopathology were benign, but tumor scrapings were positive for cancer cells, in 1 case exfoliative cytology and histopathology were positive for malignancy while tumor scrapings were benign, in 1 case only exfoliative cytology was malignant, and in 1 both cytologic examinations were negative for malignancy while histopathology was positive

Considering all 3 groups studied in general, in 39 (19 5 per cent) cytology was found positive while the pathologist found the tumor benign In 9 cases (4 5 per cent) cytology was benign and the pathologist found malignancy

CONCLUSIONS

Investigation of cancer cells in fresh, unfixed and unstained prostatic material observed under the phase-contrast microscope is recommended as a way of studying cells under conditions close to normal

The existence of surface or "in situ" cancer of the hypertrophied prostate is demonstrated

We wish to acknowledge our thanks to Dr John Janney, of the Rockefeller Foundation in Santiago, Chile, for his kind assistance

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A SEARCH FOR INHIBITORS OF PROSTATE GROWTH STIMULATORS

WILLIAM WALLACE SCOTT, WILLIAM J HOPKINS,* WENDELL M LUCAS,† AND CHARLES TESAR

Normal prostatic growth and development appear to be dependent on endogenous androgens from the testes, and there is considerable evidence to support the view that androgen administration can replace *endogenous* testicular androgen lost as a result of castration

There is much to suggest that testicular androgens are concerned with benign and malignant prostatic growth Thus, castration (presumably through removal of testicular androgens) is of benefit in the treatment of patients with benign nodular hyperplasia[1] or disseminated prostatic cancer [2] Estrogen administration is of benefit also, at least in disseminated cancer,[2] if not in benign nodular hyperplasia

Because of these responses, it is imperative that further search be made for chemical inhibitors of prostate growth stimulators

Either castration or estrogen administration will temporarily reduce known urinary metabolites of testosterone The mechanism of action of estrogen in this instance is not clear an estrogen may act to inhibit androgen production by the testes by inhibiting pituitary gonadotrophins, it may abolish synergistic action between pituitary or adrenal hormones and testicular androgens, it may antagonize androgen directly (locally at the target organ)

It has been demonstrated repeatedly that castration in man is followed by a profound increase in the urinary excretion of pituitary gonadotrophins In such instances, the administration of an estrogen in proper dosage results in reducing these gonadotrophins to normal levels

To our knowledge no one has demonstrated that the administration of an estrogen will abolish any synergistic action of pituitary or adrenal hormones and testicular androgen However, Grayhack and Scott[3] have demonstrated a synergism between pituitary luteotrophin and testosterone and Huggins and his associates[4] have shown that somatotrophin acts synergistically with testosterone

There is little evidence to support the concept that estrogen acts directly to

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antagonize testicular androgenic action Huggins believes that estrogen does "neutralize" androgen However, the experiments on which this belief was based were done in the castrate prostatic fistula dog in which exogenous testosterone was administered, and in which the pituitary and adrenal glands were intact [5]

In either instance, whether treatment of disseminated prostatic cancer consists of castration or estrogen administration, relapse is inevitable Estrogen administration is accompanied by undesirable side effects among which are gynecomastia, gastric disturbances, sodium retention and obesity with feminine distribution of fat

Partial success with present methods of endocrine treatment stimulates investigation of the mechanisms concerned and search for additional means of endocrine control of this common disease The work to be described in this paper is predicated on the theory that androgens, testicular or adrenal in origin, activate prostatic cancer

It is probable that testosterone as such is secreted by the testes Whereas little is known about the intermediate metabolism of testosterone, it is known that administration of this steroid exerts androgenic effects and that testosterone is metabolized to androsterone and etiocholanolone, both of which are excreted in the urine Thus, androgenic action takes place with minimal alteration in steroid structure

It occurred to us that one might block androgenic action by presenting the organism with a steroid which closely resembles testosterone in chemical structure but which possesses neither androgenic nor estrogenic action

If testosterone is considered to be either a substrate or a co-factor in a system whereby androgenic action occurs, theoretically, inhibition of this action could be brought about in one of several ways A chemically similar steroid might alter the normal metabolic pathway of testosterone, or block the metabolism of testosterone by flooding the system with the products of the reaction, thus reversing the enzymatic degradation Steroids of similar chemical structure might have such an affinity for the enzyme system or systems involved in androgenic response that they could act as an analog or enzyme poison

Therefore, we set about to determine any possible antiandrogenic action of a number of steroids closely related to testosterone The index of anti-androgenic action was expressed in terms of the ability of the compound tested to inhibit prostatic growth in the normal animal, when the compound was given alone, or in the castrate, when the compound was administered with a known stimulator such as testosterone Thus, it seems possible to detect antagonism of both *endogenous* and *exogenous* androgenic action

MATERIALS AND METHODS

Numerous experiments in our laboratory have shown that in the young adult castrate rat, 0 5 mg testosterone propionate, injected subcutaneously every

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TABLE 1 *Method for detecting inhibition of both* endogenous *and* exogenous *androgenic action*

Group	State of Animal	No of Rats	Testosterone* Propionate 0 5 mg	Compound under test	Objective
A	Intact	5 to 7	–	—	Control
B	Intact	5 to 7	–	2 0 mg	To test any inhibition of *endogenous* androgenic action
C	Castrate	5 to 7	–	—	Control
D	Castrate	5 to 7	+	—	To establish restorative power of *standard* dose of *exogenous* androgen
E	Castrate	5 to 7	+	0 5 mg	To test any inhibition of *exogenous* androgen
F	Castrate	5 to 7	+	1 0 mg	To test any inhibition of *exogenous* androgen
G	Castrate	5 to 7	+	2 0 mg	To test any inhibition of *exogenous* androgen
H	Castrate	5 to 7	+	5 0 mg	To test any inhibition of *exogenous* androgen

* Administered every other day for 14 days (7 injections)

other day for 2 weeks, will restore total prostate weight to that of intact controls For example, 4 to 5 weeks after castration, rats of this size will have prostates which weigh about 50 mg Castrates treated with testosterone as outlined and intact controls will have prostates which weigh 500 to 600 mg These "reconstituted" prostate glands have been found to be identical with the prostates of intact controls in terms of water content, nitrogen content and concentration and tyrosine equivalent

On the basis of these studies, 0 5 mg testosterone propionate given subcutaneously every other day for 2 weeks was chosen as the standard stimulating dose of this androgen in the castrate

The procedure used in testing each steroid was identical and was as follows All steroids were administered subcutaneously in sesame oil at a concentration of 5 mg per milliliter Each compound was tested at levels of 0 5, 1 0 and 2 0 mg every other day for 7 injections in the castrate stimulated with the standard dose of testosterone propionate, and at a level of 2 0 mg every other day for 7 injections in the intact animal Sprague-Dawley male rats, 70 to 77 days old at the beginning of the experiment and weighing approximately 200 gm, were used throughout The animals were maintained on Purina Fox Chow and water *ad libitum* Castration when used was done under ether anesthesia and 18 days allowed for atrophy of the prostate to occur before beginning the injections of steroids For each experiment, the rats were divided into 8 groups of 5 to 7 rats each as shown in table 1

Twenty-four hours after the last injection, the animals were weighed and the final weights compared with initial body weights They were then sacrificed with ether and the dorsal and ventral lobes of the prostate dissected free of fat and removed separately The individual lobes were weighed on a Roller-Smith torsion balance to the nearest 0 5 mg

TABLE 2 *Steroids tested for possible "antiandrogenic" action*

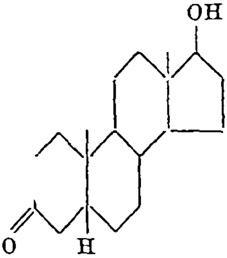
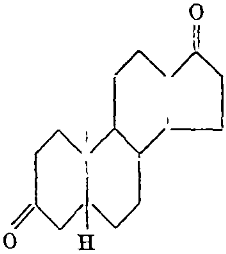
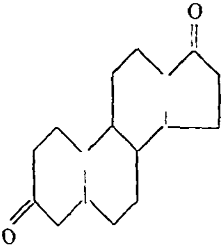
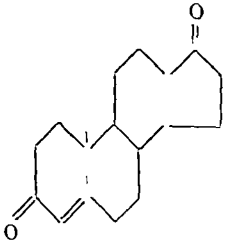
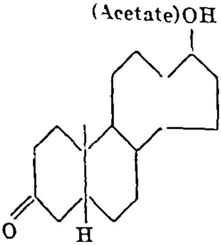
Structural Formulae	Chemical Name	Androgenicity Testosterone Propionate Equivalents	Estrogenicity	Anti Androgenicity	
				Intact animals	Castrate animals
	Etiocholan-17β-ol-3-one	1/5	0	0	0
	Androstane-3,17-dione	1/10	0	0	0
	Etiocholan-3,17-dione	0	0	0	0
	Δ^4 Androstene 3,17-dione	0	0	0	0
	Etiocholan 17β-ol 3 one acetate	0	0	0	0

TABLE 2 (*Continued*)

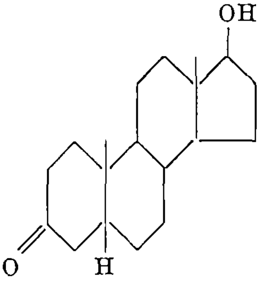
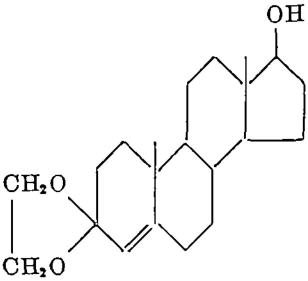
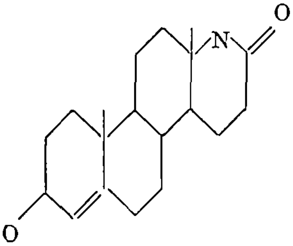
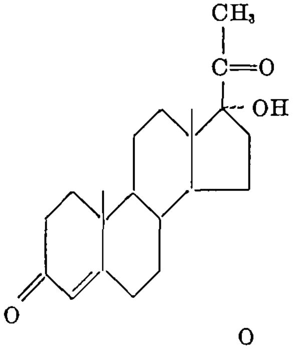
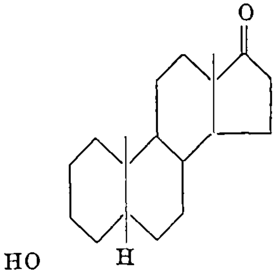
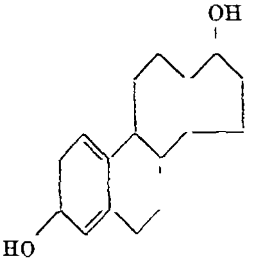
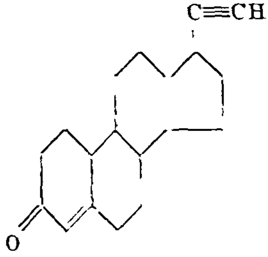
Structural Formulae	Chemical Name	Androgenicity Testosterone Propionate Equivalents	Estrogenicity	Anti Androgenicity	
				Intact animals	Castrate animals
	Androstane-17 ol-3-one	¼	0	0	0
	Testoketal	0	0	0	0
	Testolactam	0	0	0	0
	17α-hydroxy progesterone	0	0	0	0
	Etiocholan 3α ol 17-one	0	0	0	0

TABLE 2 (*Continued*)

Structural Formulae	Chemical Name	Androgenicity Testosterone Propionate Equivalents	Estrogenicity	Anti Androgenicity	
				Intact animals	Castrate animals
	Estradiol	0	—	—	[illegible]
	19-nor-ethinyl-testosterone	[illegible]	[illegible]	—	0

The compounds tested and their chemical configurations are shown in table 2 These compounds were tested during the course of a year and one-half in 7 groups of experiments Thus, it was necessary to use separate controls for each group Therefore, comparisons were made within a single group *not* between groups

Initially, in order to establish that antagonism of androgenic action could be demonstrated with this method, we first studied the effects of an estrogen, because of the previous work of others which demonstrated that an estrogen exerts an anti-androgenic action Also it seemed probable that more might be learned about the mechanism of estrogenic action by testing in this fashion

Using the method described in detail above, alpha-estradiol was tested first at levels of 0 125, 0 25 and 0 5 mg every other day for 14 days in both the young adult intact rat and in castrates receiving the standard dose of testosterone propionate (0 5 mg every other day for 14 days)

RESULTS

As tested alpha-estradiol exhibited a distinct inhibitory action on prostatic growth in the intact rat (table 3) Possibly some inhibition of prostatic growth occurred in the castrate receiving the standard stimulating dose of testosterone propionate

These results show clearly then that the administration of an estrogenic steroid can alter androgenic action and that the method of testing permits

TABLE 3 *Inhibition of* endogenous *androgenic action by an estrogen (alpha estradiol)*

Group	No of Rats	Testosterone* Propionate mg	Estradiol* mg	Prostate weight mg	Ratio of wts Prostate (mg)/Body (grams)	Change of body weight grams	Testis weight grams
Intact control	5	—	—	491	1 80	−16	
Intact	5	—	0 5	168	0 61	−26	
Castrate control	5	—	—	70	0 26	−17	—
Castrate	5	—	0 5	< castrate control		−30	—
Castrate control	5	0 5	—	778	2 71	−6	—
Castrate	5	0 5	0 5	619	2 21	2	—
Castrate	5	0 5	0 25	649	2 51	−19	—
Castrate	5	0 5	0 125	703	2 38	−20	—

* Administered every other day for 14 days

TABLE 4 *Inhibition of* endogenous *androgenic action in the young adult rat by 19 nor ethinyl-testosterone*

Group	No of Rats	Testosterone* Propionate (mg)	19 Nor* Ethinyl Testosterone (mg)	Prostate Weight (mg)	Ratio of Wts Prostate (mg)/Body (grams)	Change of Body Weight (grams)	Testis Weight (grams)
Intact control	9	—	—	534	1 59	+38	3 15
Intact	5	—	2	233	0 82	−25	2 15
Castrate control	10	—	—	32	0 10	+47	—
Castrate	6	—	2	50	0 29	−29	—
Castrate control	10	0 5	—	461	1 45	+59	—
Castrate	6	0 5	2	439	1 60	+2	—
Castrate	5	0 5	1	427	1 65	+5	—
Castrate	6	0 5	0 5	465	1 73	+9	—

* Administered every other day for 14 days

measurement of such action However, the mechanism by which inhibition is brought about remains to be determined, and immediately suggests the question Must a steroid have estrogenic properties—as commonly measured—to inhibit androgenic action?

Ten steroids whose structure is closely related to testosterone were tested for inhibition of androgenic action (table 2) To our knowledge, none of these had any estrogenic action Three were weak androgens None of the 10 steroids tested inhibited the prostate stimulating action of testosterone propionate in the castrate, nor caused a reduction in prostatic weight in the intact animal

In December 1955, through the courtesy of Dr John R Mote, a private consultant, we obtained from Chemical Specialties, Inc , a most unusual compound This compound, 19-nor-ethinyl-testosterone, is shown at the bottom of table 2

TABLE 5. *Effects of administration of 19 nor-ethinyl-testosterone to immature intact rats*

Group	Body Weight (grams)			Prostate (mg.)			Ratio of Wts., Prostate (mg.) Body (grams)	Seminal Vesicles (mg.)	Testicles (grams)	Adrenals (mg.)
	Initial	Final	Change	Ventral	Dorsal	Total				
I (11) Controls no R	102	274	−172	266	162	429	1.64	501	2.66	29
II (10) *2 mg. 19 nor-ethinyl testosterone	99	206	−107	25	24	49	0.24	67	0.38	34

* Every other day for six weeks.

Treated rats demonstrated (a) infantile scrotums, (b) abdominal testes, (c) "congested" adrenals.

As yet its properties are not clear. It is said to have progestational, estrogenic and androgenic actions, but so far we have not subjected this compound to critical tests for such actions. We can say that in the dosage used, it is not androgenic in the castrate rat.

As shown in table 4 this compound has a profound inhibitory effect on prostatic growth in the intact rat indicating inhibition of *endogenous* androgen production or action, but not *exogenous*. In the immature rat, as shown in table 5, it prevents development of the testes and scrotum, testicular descent and growth of the prostate gland and seminal vesicles. With our method of testing it acts much like an estrogen and a dosage of 2.0 mg. appears to be about equivalent to 0.5 mg. of estradiol.

It is effective by mouth and at present is being tested for its effect in patients with disseminated prostatic cancer. However, it is too early to draw conclusions.

SUMMARY

In brief, a method has been described for detecting antagonism of both *endogenous* and *exogenous* androgenic action in the rat.

An estrogenic steroid, such as estradiol, can reduce androgenic action especially *endogenous* and possibly *exogenous* but the mechanism by which this is brought about is not clear. The best explanation to us to date is that an estrogen inhibits pituitary gonadotrophins (resulting in failure of the testes to produce androgen) and certain other pituitary trophic hormones, such as prolactin, which act synergistically with testicular androgen.

A new compound has been described which effectively reduces androgenic action. Whether this is the result of estrogenic properties remains to be determined.

In conclusion, we wish to emphasize that this represents a progress report. Currently, 15 additional compounds are under test.

What a glorious day it will be for urology when we can shrink the benign nodular hyperplastic prostate, quiet the carcinomatous one and increase libido and potentia all with a tablet. Oh happy day.

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SEXUAL POTENCY AFTER PERINEAL BIOPSY

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A latent drawback to projected perineal prostatic surgery is the possibility of postoperative sexual impotence Of complications which may attend the perineal approach to the prostate, this seems the most unpredictable and least related to the technique of the operation or the skill of the surgeon The importance to the physician, of being able to provide the patient with an accurate appraisal of effects of perineal surgery on potency, is self evident and was the stimulus for this study In the young adult male the possibility of loss of potency may be a formidable psychological barrier against surgery Elderly men may become deeply concerned when confronted with this possibility Although it is recognized that this should not be a deterrent when the procedure is indicated, as in suspected prostatic malignancy, it seemed desirable to have some data concerning the frequency of this complication in relation to perineal surgery

Young in describing his results of perineal prostatectomy said, "Of those whose sexual powers were described as 'normal' before operation, 80 per cent retained them afterward Of those in whom they were 'diminished' less than half retained them after operation but in this number were some who showed improvement over the condition before operation Of those whose sexual powers were 'absent' before operation, practically all remained in the same condition afterward" Hudson, and others (1954) stated, "open perineal biopsy has not produced either urinary incontinence or sexual impotence" Pearlman (1955) felt that the perineal approach for biopsy is followed by some diminution of libido

The purpose of this present study is to try to assess the effect of open perineal prostatic biopsy on potency In an attempt to observe this in a more or less "pure culture" without the possible side effects of malignant or other disease or of other operative procedures, this study concerns results in patients who had open perineal biopsy for suspected carcinoma but in whom the findings were normal and no further significant procedure was done

METHODS

The study embraces a period between September 1951 and December 1953, during which 75 patients were subjected to perineal prostatic biopsy Many of these were found to have carcinoma of the prostate requiring total excision of the prostate and seminal vesicles Others had orchiectomy and/or estrogen therapy for advanced carcinoma Simple perineal prostatic enucleation was performed in some cases for benign hypertrophy However, it was possible to find within this group of 75 patients 24 who had no significant further surgical or medical treatment of the prostate Three had subsequent transurethral prostatic resection for removal of obstructive tissue Perineal prostatic needle biopsy had been

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FIG 1 Work sheet Study of potency following open perineal prostatic biopsy

A Information derived from hospital record

- Name
- Hospital number
- Age
- Marital status
- Indication for operation
- Needle biopsy performed
- Date of operation
- Surgeon
- Type of approach
- Complication
  - Rectal laceration
  - Perineal fistula
  - Incontinence (urinary or rectal)
  - Other (systemic)
- Healing time
- Catheter time
- Hospital days
- Final pathological diagnosis
- Further treatment

B Information derived from personal interview

Duration of followup

	Preoperative	Postoperative
Potency frequency and ability		
Intercourse frequency		
Ejaculation		
Orgasm presence or absence		
Perineal discomfort amount and duration		

performed on almost all of these patients without evidence of carcinoma, before the open perineal biopsy (Kaufman and others 1954) Open perineal prostatic biopsy was then performed by one of the resident staff or by one of the consulting staff Although the residents were learning the operation, no correlation could be made between the surgeon and postoperative potency of the patient as judged from this small series

The 24 patients who had simple biopsy were personally interviewed and all asked the same questions as outlined in the work sheet (fig 1) These interviews were undertaken after the surgery, and it was not always possible to be certain of the validity of the patient's memory of his potency prior to operation However, an earnest attempt was made on the part of the interviewer as well as the patient to appraise pre- and postoperative potency accurately The duration of followup observation ranged from 4 to 26 months In addition to questions concerning ability to have erections, each patient was questioned as to frequency of intercourse and the presence or absence of orgasm and ejaculation before and after surgery Other questions concerned the amount and duration of perineal discomfort

The psychic and gonadal components of potency did not seem within the scope of this study The neuromuscular components of potency have been well summarized by Munro and others (1948) and Whitelow and Smithwick (1951) It was our hope that by limiting the group of patients studied to those who had simple biopsy without other significant procedures, the effects of the operation itself on this neuromuscular component could be evaluated without other extraneous factors

On the basis of the information derived from this questionnaire on each patient, the cases were classified as follows no change, or increase, diminution or total loss in potency—i e , ability to have erections, intercourse, and orgasm

RESULTS

One-third of the patients (7 unchanged, 1 "increased") had no change or increase in potency Thirty-seven and one-half per cent (9 patients) claimed diminution of potency after perineal biopsy And 29 per cent (7 patients) had complete loss of potency (table 3, 4, and 5)

Age (See table 1) The age of these patients ranged from 32 to 79 years with an average of 58 years An apparent relationship seemed to exist between age of the patient and postoperative potency The older the patient, the more apt he was to have diminution or loss of potency In general, patients under the age of 60 had a better chance of having their potency remain unchanged or being a little diminished In the group suffering complete loss, the average age was 64 4, whereas in the group in which potency was not changed, the average age was 53 7 (range, 32 to 71 years)

Type of approach Young's approach to the prostate was used 5 times and Belt's approach was used 19 times In this small series there did not seem to be any relationship between type of approach and postoperative potency (table 2)

Postoperative management and pathology All patients were placed on urethral catheter drainage which was maintained for an average of 6 9 days The microscopic diagnosis of the biopsy material was found to be fibroadenomatous hyperplasia, with or without chronic prostatitis in 21 patients One patient had nonspecific prostatitis, one patient was found to have a leiomyoma, and one patient had a nonspecific granuloma There did not seem to be any correlation between the pathological process and postoperative potency

Complications Ten of the 24 patients had a complication either during or after operation One patient developed tachycardia while in the exaggerated lithotomy position One patient had a hypotensive episode accompanied by electrocardio-

TABLE 1 *Correlation between age at time of surgery and postoperative potency*

Per cent of Total	Postoperative Potency	Age at Time of Surgery	Average Age
29% } 33%	Unchanged (7)	32, 59, 63, 56 58, 54, 54	53 7
4% }	Increase (1)	58	58
37%	Diminution (9)	59, 65, 71, 53, 55, 56, 50, 60 61	58 8
29%	Complete loss (7)	66, 64 58, 63, 79, 56, 65	64 4

TABLE 2 *Correlation between type of approach and postoperative potency*

Postoperative Potency	Young	Belt
Unchanged	2	5
Increase	0	1
Diminution	1	8
Complete loss	2	5

TABLE 3 *Group A Unchanged postoperative potency (*Includes one with increase) (8 patients, 33%)*

Patient Number	43269	31183	37617	37547	33464	34688	39800	37746
Age	32	59	63	56	58	54	54	58
Marital Status (D—divorced S—single M—married W—widower)	S	M	M	M	M	Div	M	M
Indication for operation	Nodule base of prostate	Nodule left lobe	Nodule	Nodule	Firm induration both lobes	Firm rt lobe	Nodule	Nodules both lobes
Needle biopsy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date of operation	11 9 53	3 31 52	8 5 53	1 7 53	10 17 52	12 10 52	5 6 53	1 21 53
Surgeon, resident or consultant	C	R	R	R	R	R	R	R
Type of approach	Belt	Young	Young	Belt	Belt	Belt	Belt	Belt
Complication	Laceration of rectum	None—hemorrhoids	B P Fall 2 hrs after surgery EKG ischemia	None	None	None	Laceration of rectum	None
Healing time	23 days	12 days	22 days	7 days	6 days	7 days	39 days	10 days
Catheter time	5 days	4 days	13 days	3 days	7 days	5 days	14 days	18 days
Hospital days	9 days	12 days	22 days	14 days	11 days	12 days	34 days	23 days
Perineal pain	Slight for 3 weeks	Slight discomfort 5–6 mos	Slight discomfort 1 mo	Slight for 2 weeks	Slight for 2 mos	None after 1 mo	For 2 mos	Slight 9 days
Final pathological diagnosis	Fibromuscular and non specific inflammation	Fibroadenomatous hyperplasia calcific concretions	Adenomatous hyperplasia sclerosis of arteries	Leiomyoma	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia
Further treatment	TUR	None	None	None	None	None	None	TUR
Duration of followup	(4 mos)	26½ mos	10 mos	17 mos	20 mos	18 mos	13½ mos	17 mos
Preoperative potency	2 x week	Daily	1–2 x year	1 x week	1–2 x week	2–3 x week	2 x mos	2–3 x mos
Intercourse	2 x week	1–3 x week	None	1 x week	1–2 x week	None	2 x mos	2–3 mos
Orgasm	Yes	Yes	None	Yes	Yes	None	Yes	Yes
Postoperative potency	2 x week	Daily	1–2 x year	1 x week	1–2 x week	2–3 x week	2 x mos	1 x week
Intercourse	2 x week	1–3 x week	None	1 x week	1–2 x week	None	2 x mos	1 x week
Orgasm	Yes	Yes	None	Yes	Yes	None	Yes	Yes
Comments					4 mos P O before erection		intercourse 2 mos P O normal in 4 mos	increase receiving Vi E

TABLE 4 *Group B Diminished postoperative potency (9 patients, 37%)*

Patient Number	12572	40621	35077	35236	37843	38765	34355	74590	71444
Age	59	65	71	53	61	55	56	50	60
Marital Status (S—single M—married W—widower)	W	M	M	M	M	M	M	M	M
Indication for operation	Induration left lobe	Nodule	Nodular prostate	Nodules	Nodule	Nodule left lobe	Nodule Rt lobe	Nodule at apex	Nodule
Needle biopsy	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Date of operation	10–1–52	6–17–53	9–10–52	10–1–52	2–9–52	3–11–53	9–24–52	10–30–53	7–20–53
Surgeon, resident or consultant	R	R	C	C	R	C	R	C	C
Type of approach	Belt	Belt	Belt	Belt	Belt	Young	Belt	Belt	Belt
Complication	None	None	None	None	Perineal bleeding	Thromophlebitis left leg	Stitch abscess	None	Rectal laceration
Healing time	7 days	7 days	7 days	10 days	22 days	6 days	9 days	6 days	8 days
Catheter time	6 days	7 days	5 days	10 days	3 days	8 days	5 days	7 days	7 days
Hospital days	12 days	12 days	16 days (consultations)	12 days	29 days	50 days	12 days	9 days	8 days
Perineal pain	Minimal 2 mos	2 mos	None	None	Slight 1 mo	Slight 1 mo	Pain 6 weeks (tender 1 year)	1 mo	None
Final pathological diagnosis	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Granulomatous prostatitis	Benign hypertrophy	Encapsulated fibroadenoma	Nodular hyperplasia
Further treatment	None	None	None	None	None	None	None	None	None
Duration of followup	20 mos	12 mos	21 mos	20 mos	16 mos	15 mos	21 mos	20 mos	24 mos
Preoperative potency	3–4 x week	3–4 x week	2 x mos	1 x week	2 x mos	1 x mo	3 x mos	3 x week	1 x week

Intercourse	3-4 x week	2 x week	2 x mos	2 x mos	0	1 x mo	2 x week	2-3 x week	3-4 x mos
Orgasm	Yes	Yes	Yes	Yes	0	Yes	Yes	Yes	Yes
Postoperative potency	1 x week (weak)	1 x mo (weak)	1-2 x mos	1 x week (weak)	1 x mo	10 x yr	1 x yr	1 x week	1 x mo
Intercourse	None	None	1 x mo	None	0	10 x yr	1 x yr	1 x week	1 x mo
Orgasm	None	None	Yes	Yes	0	Yes	Yes	Yes	Yes
Comments	no desire	Int satisfactory erection 12 mos P O		psychic component expressed by patient		Return to normal 4 mos P O	Lacks desire		Intercourse 4 weeks P O Lacks desire

TABLE 4 *Group B Diminished postoperative potency (9 patients, 37%)*

Patient Number	12572	40621	35077	35236	37843	38765	34355	74590	71444
Age	59	65	71	53	61	55	56	50	60
Marital Status (S—single M—married W—widower)	W	M	M	M	M	M	M	M	M
Indication for operation	Induration left lobe	Nodule	Nodular prostate	Nodules	Nodule	Nodule left lobe	Nodule Rt lobe	Nodule at apex	Nodule
Needle biopsy	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Date of operation	10–1–52	6–17–53	9–10–52	10–1–52	2–9–52	3–11–53	9–24–52	10–30–53	7–20–53
Surgeon, resident or consultant	R	R	C	C	R	C	R	C	C
Type of approach	Belt	Belt	Belt	Belt	Belt	Young	Belt	Belt	Belt
Complication	None	None	None	None	Perineal bleeding	Thromophlebitis left leg	Stitch abscess	None	Rectal laceration
Healing time	7 days	7 days	7 days	10 days	22 days	6 days	9 days	6 days	8 days
Catheter time	6 days	7 days	5 days	10 days	3 days	8 days	5 days	7 days	7 days
Hospital days	12 days	12 days	16 days (consultations)	12 days	29 days	50 days	Pain 6 weeks (tender 1 year)	9 days	8 days
Perineal pain	Minimal 2 mos	2 mos	None	None	Slight 1 mo	Slight 1 mo	12 days	1 mo	None
Final pathological diagnosis	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Granulomatous prostatitis	Benign hypertrophy	Encapsulated fibroadenoma	Nodular hyperplasia
Further treatment	None	None	None	None	None	None	None	None	None
Duration of followup	20 mos	12 mos	21 mos	20 mos	16 mos	15 mos	21 mos	20 mos	24 mos
Preoperative potency	3–4 × week	3–4 × week	2 × mos	1 × week	2 × mos	1 × mo	3 × mos	3 × week	1 × week

Intercourse	3 1 x week	2 x week	2 x mos	2 x mos	0	1 x mo	2 x week	2 3 x week	1 1 x mos
Orgasm	Yes	Yes	Yes	Yes	0	Yes	Yes	Yes	Yes
Postoperative potency	1 x week (weak)	1 x mo (weak)	1 2 x mos	1 x week (weak)	1 x mo	1 5 x yr	1 x yr	1 x week	1 x mo
Intercourse	None	None	1 x mo	None	0	1-5 x yr	1 x yr	1 x week	1 x mo
Orgasm	None	None	Yes	Yes	0	Yes	Yes	Yes	Yes
Comments	no desire	1st satisfactory erection 12 mos P O		psychic component expressed by patient		Return to normal 1 mos P O	Lacks desire		Intercourse 3 weeks P O Lacks desire

TABLE 4 *Group B Diminished postoperative potency (9 patients, 37%)*

Patient Number	12572	40621	35077	35236	37843	38765	34355	74590	71444
Age	59	65	71	53	61	55	56	50	60
Marital Status (S—single M—married W—widower)	W	M	M	M	M	M	M	M	M
Indication for operation	Induration left lobe	Nodule	Nodular prostate	Nodules	Nodule	Nodule left lobe	Nodule Rt lobe	Nodule at apex	Nodule
Needle biopsy	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Date of operation	10–1–52	6–17–53	9–10–52	10–1–52	2–9–52	3–11–53	9–24–52	10–30–53	7–20–53
Surgeon, resident or consultant	R	R	C	C	R	C	R	C	C
Type of approach	Belt	Belt	Belt	Belt	Belt	Young	Belt	Belt	Belt
Complication	None	None	None	None	Perineal bleeding	Thromophlebitis left leg	Stitch abscess	None	Rectal laceration
Healing time	7 days	7 days	7 days	10 days	22 days	6 days	9 days	6 days	8 days
Catheter time	6 days	7 days	5 days	10 days	3 days	8 days	5 days	7 days	7 days
Hospital days	12 days	12 days	16 days (consultations)	12 days	29 days	50 days	Pain 6 weeks (tender 1 year)	9 days	8 days
Perineal pain	Minimal 2 mos	2 mos	None	None	Slight 1 mo	Slight 1 mo	12 days	1 mo	None
Final pathological diagnosis	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Granulomatous prostatitis	Benign hypertrophy	Encapsulated fibroadenoma	Nodular hyperplasia
Further treatment	None	None	None	None	None	None	None	None	None
Duration of followup	20 mos	12 mos	21 mos	20 mos	16 mos	15 mos	21 mos	20 mos	24 mos
Preoperative potency	3–4 × week	3–4 × week	2 × mos	1 × week	2 × mos	1 × mo	3 × mos	3 × week	1 × week

graphic changes consistent with anterior wall ischemia 2 hours after surgery. Three patients had lacerations of the rectum which were identified and repaired during surgery. One of these patients required 39 days to heal the perineal wound. Two patients had persistent perineal bleeding of slight degree for one and two months. One patient had a small incisional abscess. Two major complications occurred. In one patient thrombophlebitis developed requiring 50 days of hospitalization before complete recovery. In another slight stress incontinence of urine and a relaxed anal sphincter developed which caused him to soil himself occasionally. There were no deaths.

Tables 3, 4 and 5 represent the complete information accumulated in the three groups: group A, unchanged or increased postoperative potency; group B, diminished postoperative potency; and group C, postoperative loss of potency. In general, there seemed to be little correlation between the complications and potency, although when these tables are viewed altogether it would appear that the patients in table 5 (group C—postoperative loss of potency) had a few more instances of perineal bleeding or prolonged drainage. This may or may not be significant; it is difficult to evaluate in this small series. Our general impression was that loss or decrease in potency could not be predicated on the basis of whether or not the patient had a complication.

DISCUSSION

It is difficult to feel confident that results in only 24 cases are representative of all patients having open perineal prostatic biopsy. However, a trend seemed to be established in this study, and it was hoped that the fact that these patients were "pure examples" of perineal exposure and biopsy without other conditions or significant surgery might add to the validity of the small series. A serious defect in compilation of this material was the fact that most of the results on the questionnaire were gathered after the surgery, and memory had to be trusted concerning answers to questions about potency before surgery. A better way to do a study of this sort would be to have accurate information before surgery was ever undertaken and then compare it with a careful interview some months later.

If this study means anything, the only positive correlation we can see concerns the patient's age. As mentioned earlier, patients under 60 seem to have a better chance of retaining their potency or having diminution, whereas those over 60 are more apt to have a complete loss. Although this figure is probably variable, we find it comforting to make reference to this study in discussing the problem with patients.

It seems mandatory whenever perineal surgery is planned to raise the question of potency. When dealing with the problem of possible carcinoma (which was the reason for biopsy in all these cases) the situation may be formulated somewhat as follows, If there is a carcinoma of the prostate present, appropriate treatment whether it be total prostatectomy or orchiectomy and estrogen therapy will result in impotence. This is probably the only unavoidable drawback of proper treatment for cancer of the prostate. If, on the other hand, it develops

TABLE 5 *Group C Postoperative loss of potency (7 patients, 29%)*

Patient Number	10595	20356	37497	37012	35104	32135	35078
Age	66	64	58	63	79	56	65
Marital status (S—single M—married W—widower D—divorced)	M	M	S	M	M	W	Div
Indication for operation	Firm left lobe	Nodular prostate	Indurated prostate	Nodular prostate	Hard irregular prostate	Induration	Nodule Rt Lobe
Needle biopsy	None	Yes	Yes	Yes	Yes	Yes	Yes
Date of operation	7-22-53	10-7-53	1-14-53	11-4-53	9-10-52	7-8-52	9-10-52
Surgeon, resident or consultant	R	R	C	R	C	C	C
Type of approach	Young	Young	Belt	Belt	Belt	Belt	Belt
Complication	Stitch Abscess Tachycardia	Perineal bleeding 2 mos	Drainage 1½ weeks	Drainage 2 weeks	B P drop Pain in flank	None	Slight urinary stress incontinence Relaxed anal sphincter
Healing time	11 days	6 days	1½ weeks	14 days	6 days	6 days	7 days
Catheter time	10 days	9 days	14 days	2 days	5 days	3 days	11 days
Hospital days	15 days	12 days	19 days	8 days	9 days	7 days	14 days
Perineal pain	Minimal	Slight tenderness	Slight 1 mo	Slight 3 weeks	Minimal 2 weeks	None	None
Final pathological diagnosis	Adenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Fibroadenomatous hyperplasia	Benign hyperplasia	Fibrosis	Fibroadenomatous hyperplasia
Further treatment	TUR	None	None	None	None	None	None
Duration of follow up	7½ mos	19½ mos	16 mos	7 mos	21 mos	23 mos	21 mos
Preoperative potency	3 × week	3-4 × week	1 × mo	2 × week	6 × yr	2 × week	Daily
Intercourse	3 × week	3-4 × week	1 × mo	1-2 × week	0	2 × week	2-3 × mos
Orgasm	Yes	Yes	Yes	Yes	0	Yes	Yes
Postoperative potency	0	0	0	0	0	0	0
Intercourse	0	0	0	0	0	0	0
Orgasm	0	0	0	0	0	0	0
Comments	No desire	Has desire	Has desire			Occasionally has desire	

KAUFMAN, J J , ROSENTHAL, M AND GOODWIN, W E Methods of diagnosis of carcinoma of the prostate A comparison of clinical impression, prostatic smear, needle biopsy, open perineal biopsy and transurethral biopsy J Urol , **72** 450–465, 1954
MUNRO, D HORNE, H H , JR AND PAULL D P The effect of injury to the spinal cord and cauda equina on the sexual potency of men New Eng J Med **239** 903, 1948
PEARLMAN, C K Transrectal biopsy of the prostate Trans West Sect Am Urol Assoc , **22** 125–130, 1955
WHITELOW, G P AND SMITHWICK R Some secondary effects of sympathectomy with particular reference to disturbance of sexual function New Eng J Med **245** 121, 1951
YOUNG, H H AND DAVIS, D M Young's Practice of Urology Philadelphia W B Saunders Co , 1926

that you do not have a cancer of the prostate, you have some chance of losing your sexual power or suffering a decrease of it after perineal prostatic biopsy In a small group of cases that have been studied, less than 30 per cent had a complete loss of sexual power This was more likely to happen in older patients About 40 per cent had some decrease in sexual power, whereas one-third had their sexual power unchanged or increased When *you are considering this operation, you* have to realize that you are taking this chance " When this feeling is expressed, perineal biopsy is not done casually, and it is not done unless there is a reasonable likelihood that prostatic carcinoma may exist

This study purposely excluded data on the degree or frequency of loss of potency following other perineal operations on the prostate It would be important to carry out such a study on all types of operations on the prostate The questionnaire should be filled out before and after surgery

The difference between the results of this study and the results reported by Hudson, and others, who noted no change in sexual function, is difficult to explain Possible factors might be difference in surgical technique or, more likely, difference in method of evaluation of the factor of sexual potency It would be important in any future study to make a careful comparison and evaluation of similar patients done in different institutions

SUMMARY

An attempt was made to evaluate sexual potency before and after simple perineal exposure and biopsy of the prostate gland Twenty-four patients with suspected prostatic nodules, later proven to be benign, had open perineal prostatic biopsy without any further significant treatment

Although the series is small, the patients seemed roughly to fall into three groups with about equal distribution Twenty-nine per cent (7) of the patients became totally impotent Thirty-seven and one-half per cent (9) showed a diminution in sexual power One-third (8 patients) claimed unchanged or increased potency Patients under sixty seemed to have a better chance of retaining potency The average age of those who suffered complete loss was 64 4 years, whereas the average age of those whose potency was unchanged or increased was 53 7 years The route of perineal approach and skill of the operator did not seem to be factors in the end-results More of the patients who had a complete postoperative loss of potency had complications related to the perineal wound, such as drainage or bleeding postoperatively

Probably perineal surgery *per se* has some effect on postoperative sexual potency This problem should be studied further with a larger group of patients and careful questioning before and after surgery

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DIAGNOSTIC RATINGS

Methods of rating Two readers rated the examinations independently The contrast media were unknown The scale was 0 to 4 One reader (M R) rated the calyces, pelves, and ureters separately for each upper tract The other rated the over-all appearance for opacity and filling There were two methods of rating

1 *Classification by grade* The opinions of the readers were averaged for each examination The grades are as follows

Excellent Rating 3+ to 4 Visualization comparable to a retrograde study

Good Rating 2+ to 3 Visibility and opacity sufficient for diagnosis so that a retrograde study would not be required

Fair Rating 1+ to 2 Visualization incomplete for diagnosis but adequate for determination of function and the presence or absence of obstruction

Poor Rating 1 or less Unsatisfactory study

Diagnostic Examinations classified as Excellent and Good

Undiagnostic Examinations classified as Fair and Poor

Reference to our series in tables 2 and 3 showed that there was about the same percentage of diagnostic and nondiagnostic films for urokon 50 and 70, and hypaque However, there were more excellent examinations with hypaque Diodrast had nearly the same percentage of excellent studies as urokon 50, but fewer were diagnostic The poorest results were with urokon 30

Our data for table 3 were subjected to statistical study using the Chi-squared method of testing The findings are tabulated in table 4

The diagnostic and nondiagnostic ureters in our series are compared in table 5 and the Chi-squared analyses for them are in table 6 The data indicate that filling is best with hypaque

2 *Mean ratings* The mean diagnostic ratings for each of the iodide compounds were determined separately by the two panel members and recorded in table 7 Hypaque has the highest ratings It is of interest to note that the poor values for the ureters in the urokon group is the principal factor in reducing their average visibility The average ratings for the two readers are plotted in figure 1 Although the differences range from 0 47 to 0 57, they fall along a 45° slope with an average displacement of 0 52 along the abscissa, due to higher values given by one of the readers (T N) The correlation of the observations supports the validity of the study Figure 2 plots the ratings of one reader (M R) against the molecular concentration expressed in moles per ampule Figure 3 plots these ratings against the iodine content in grams per ampule A family of asymptomatic curves is derived by connecting similar points for the three urokon media and projecting them back to zero The curves increase rapidly to urokon 30, then more slowly to urokon 50 and 70 The resemblance to a renal clearance curve is striking, suggesting a rapid rise until the tubular maximum is reached, and then a leveling off when excretion is principally by glomerular filtration If the correlation can be made, the tubular maximum is reached at least by the molecular concentration for urokon 30

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COMPARATIVE STUDY OF FIVE UROGRAPHIC CONTRAST MEDIA

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The first of the diodopyridones successfully used for intravenous pyelography was 35 per cent diodrast This was followed by 50 per cent neo-iopax The diagnostic quality of examinations using neo-iopax was about the same as for diodrast but it had the disadvantage of not infrequently causing leakage pain and vein cramp (Mullen and Hughes) The advent of the triiodobenzoates represented an advance in chemistry The media of this group urokon, hypaque, miokon, are all sodium salts and differ only in the side chains in the 3 5 position Reports (Bohne and Christeson, Mullen and Hughes, Nesbit and Nesbitt) indicated that the diagnostic quality of urokon 30, the first of these, was below that of 35 per cent diodrast This was rectified by the introduction of the 50 and 70 per cent solutions The newest member of the triiodobenzoate group is renografin It differs from hypaque only in that it is a mixture of methylglucamine and sodium salts in a ratio of 6 6 to 1 The methylglucamine increases the solubility of the compound above the 50 per cent maximum for the sodium salt alone The formulae and other data for the iodide media are in table 1

There have been many clinical studies of the various iodide compounds for diagnostic quality and side effects Most of them are limited to one or two media In general, comparison of these studies is unsatisfactory because they are subjective and lack universal standards The results of some of them are summarized in table 2 Ours are included with them Reports for miokon and renografin are omitted since they are not pertinent to this paper

PROCEDURE

The study began in March 1955 and continued for a year Four hundred twenty examinations were reviewed Fifty per cent hypaque, thirty-five per cent diodrast, and 30, 50 and 70 per cent urokon were rotated without selection of patients When a medium was out of supply, the others were continued in rotation until it was replaced

Two ounces of castor oil were given at 2 00 p m the day before the examination, followed in 4 hours by a cleansing enema Food and fluids were withheld after midnight The next morning each patient was questioned for allergy and iodine sensitivity Testing was limited to an intravenous injection of 1 ml of the medium to be used since other methods are probably less reliable If there was no reaction to the test in a half hour, the patient was logged on a daily urogram sheet and the examination was done Reactions, if any, were recorded The radiologist was especially on guard for emergency measures if there was any history of allergy or iodine sensitivity Preliminary antihistaminics were not used Injection time was 1 to 3 minutes The procedures were done without compression

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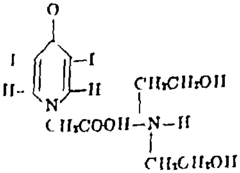
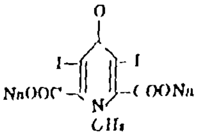
Diodrast† (Iodopyracet)	3 5 diiodo 4 pyridone N acetic acid diethanolamine ($C_{11}H_{16}I_2N_2O_5$)		35	30	186 0	0 0216	49 8	17 5	5 25
Neo iopax‡ (sodium iodomethamate)	Disodium 1 Methyl 3 5 diiodo 4 pyridone 2 6 dicarboxylate ($C_8H_3I_2NO_5Na_2$)		50	20	103 0	0 0215	51 5	25 9	5 15

* Data obtained from commercial literature

† Available also in 10 and 20 cc ampules as 35% and 30 cc ampules as 70% solution

‡ Available also in 30 cc ampules as 50% and 20 and 50 cc ampules as 75% solution

TABLE 1 * *Characteristics of the media*

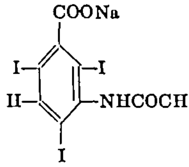
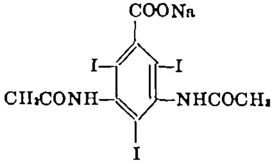
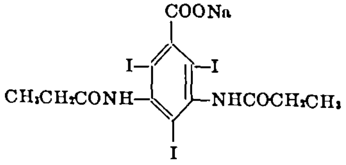
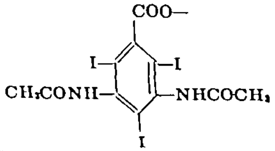
Brand Name	Formula	Chemical Structure	% Soln	cc/amp	Mol Wt	Moles per amp	% I/mol	% I/soln	Gm I/amp
Urokon 30 (sodium acetrizoate)	Sodium 3 acetylamino 2 4 6 triiodobenzoate ($C_9H_5I_3NO_3Na$)		30	25	578 9	0 0129	65 8	19 7	4 94
Urokon 50	Do	Do	50	25	578 9	0 0216	65 8	32 9	8 23
Urokon 70	Do	Do	70	25	578 9	0 0303	65 8	46 1	11 50
Hypaque (sodium diatrizoate)	Sodium 3-diacetylamino 2 4 6 triiodobenzoate ($C_{11}H_8I_3N_2O_4Na$)		50	30	636 0	0 0236	50 87	29 9	8 97
Miokon (sodium diprotrizoate)	Sodium 3 5-dipropionyl amino 2 4 6 triiodo benzoate ($C_{13}H_{12}I_3N_2O_4Na$)		50	30	663 98	0 0226	57 3	28 7	8 60
Renografin (sodium and methyl glucamine salts of diatrizoate)	10% Sodium 3 5-diacetylamino 2 4 6 triiodobenzoate ($C_{11}H_8I_3N_2O_4Na$) 60% Methylglucamine 3 5 diacetylamino 2 4 6 triiodobenzoate ($C_{18}H_{26}I_3N_3O_9$)	Na^+ $C_7H_{17}O_5N^+$ 	76	20	(613 8 H) 636 0 Na 809 0 Meg	0 0032 Na 0 0163 Meg 0 0195 Tot	(62 1 H) 59 87 Na 47 0 Meg	6 0 Na 30 9 Meg 36 9 Tot	73 8

TABLE 4 *Chi squared probabilities for comparison of differences of diagnostic vs nondiagnostic examinations*

	Urokon 30 35D—40ND	Urokon 50 67D—28ND	Urokon 70 64D—23ND	Hypaque 50 69D—28ND	Diodrast 35 38D—28ND
Urokon 30	—	$\chi^2 = 9.92$ $p < .01$	$\chi^2 = 12.04$ $p < .001$	$\chi^2 = 10.56$ $p < .01$	$\chi^2 = 1.67$ $p < .20$
Urokon 50	$\chi^2 = 9.92$ $p < .01$	—	$\chi^2 = .027$ $p < .90$	$\chi^2 = .008$ $p < .95$	$\chi^2 = 2.93$ $p < .10$
Urokon 70	$\chi^2 = 12.04$ $p < .001$	$\chi^2 = .027$ $p < .90$	—	$\chi^2 = .136$ $p < .80$	$\chi^2 = 4.29$ $p < .05$
Hypaque 50	$\chi^2 = 10.56$ $p < .01$	$\chi^2 = .008$ $p < .95$	$\chi^2 = .136$ $p < .80$	—	$\chi^2 = 3.68$ $p < .10$
Diodrast 35	$\chi^2 = 1.67$ $p < .20$	$\chi^2 = 2.93$ $p < .10$	$\chi^2 = 4.29$ $p < .05$	$\chi^2 = 3.68$ $p < .10$	—

TABLE 5 *Comparison of diagnostic and nondiagnostic ureters*

	Medium				
	Urokon 30	Urokon 50	Urokon 70	Hypaque 50	Diodrast 35
No Patients	75	95	87	97	66
% Diagnostic	10.7	28.4	31.0	42.3	27.2
% Nondiagnostic	89.3	71.6	69.0	57.7	72.8

TABLE 6 *Chi squared probabilities for comparison of differences of diagnostic vs nondiagnostic ureters*

	Urokon 30 8D—67ND	Urokon 50 27D—68ND	Urokon 70 27D—60ND	Hypaque 50 41D—56ND	Diodrast 35 18D—48ND
Urokon 30	—	$\chi^2 = 8.15$ $p < .01$	$\chi^2 = 9.88$ $p < .01$	$\chi^2 = 22.80$ $p < .001$	$\chi^2 = 6.40$ $p < .02$
Urokon 50	$\chi^2 = 8.15$ $p < .01$	—	$\chi^2 = .015$ $p < .90$	$\chi^2 = 4.00$ $p < .05$	$\chi^2 = .032$ $p < .90$
Urokon 70	$\chi^2 = 9.88$ $p < .01$	$\chi^2 = .015$ $p < .90$	—	$\chi^2 = 2.52$ $p < .20$	$\chi^2 = .079$ $p < .80$
Hypaque 50	$\chi^2 = 22.80$ $p < .001$	$\chi^2 = 4.00$ $p < .05$	$\chi^2 = 2.52$ $p < .20$	—	$\chi^2 = 2.40$ $p < .20$
Diodrast 35	$\chi^2 = 6.40$ $p < .02$	$\chi^2 = .032$ $p < .90$	$\chi^2 = .079$ $p < .80$	$\chi^2 = 2.40$ $p < .20$	—

TABLE 7 *Mean ratings*

Medium	Patients	Roth				Nicholson			Combined	Difference
		Visibility of			Average visibility	Opacity	Filling	Average visibility	Average visibility	Average visibility
		Calyces	Pelves	Ureters						
Urokon 30	75	1.95	1.95	1.23	1.71	2.29	2.27	2.28	2.00	.57
Urokon 50	95	2.30	2.36	1.63	2.09	2.66	2.58	2.62	2.36	.53
Urokon 70	87	2.42	2.45	1.76	2.21	2.81	2.75	2.78	2.50	.57
Hypaque 50	97	2.45	2.52	2.04	2.39	2.90	2.83	2.87	2.61	.48
Diodrast 35	66	2.06	2.09	1.70	1.95	2.37	2.48	2.42	2.19	.47

TABLE 2 *Comparison of studies*

Medium	Authors	Inj Time (Minutes)	Compression	Diagnostic Rating: Number patients	% exc	% good	% fair	% poor	Reactions: Number patients	% pts one or more reactions	% pts local reaction
Urokon 30	Roth and Nicholson	1–3	No	75	8 0	38 7	38 7	14 6	75	10 1	2 [illegible]
Urokon 30	Nesbitt and Nesbitt	Not reported	Not reported	1000	64 0		25 0	11 0	1000	18 0	
Urokon 30	Bohne and Christeson	1–2	Not reported	100		33 0	52 0	15 0	100	4 0	
Urokon 50	Roth and Nicholson	1–3	No	95	16 8	53 7	22 1	7 4	95	26 3	13 [illegible]
Urokon 50	Strittmatter	1–2	Yes	250	37 6	45 2	12 4	4 8	227*	49 0	
Urokon 70	Roth and Nicholson	1–3	No	87	21 9	51 6	21 9	4 6	87	39 1	26 4
Urokon 70	Nesbitt and Nesbitt	Not reported	Not reported	585	34 0	45 0	14 0	7 0	585	55 0	
Urokon 70	Bohne and Christeson	1–2	Not reported	100		69 0	24 0	7 0	35	17 0	
Urokon 70	Byrne and Melick	1–2	Yes	500		77 0	9 0	14 0	250	30 0	
Hypaque 50	Roth and Nicholson	1–3	No	97	35 1	36 1	23 7	5 1	97	14 5	9 3
Hypaque 50	Bodner et al	1–2	No	300	72 6	18 6	5 4	3 4	300	7 0	
Hypaque 50	Lowman et al	Not reported	Yes	300	85 0		15 0		300	7 7	0
Hypaque 50	Moore and Mayer	Average 3	Yes	210	74 8	18 1	7 1		210	13 3	0
Hypaque 50	Root and Strittmatter	1–3	Yes	350	43 5	47 1	6 9	2 5	350	9 7	
Diodrast 35†	Roth and Nicholson	1–3	No	66	15 2	42 4	31 8	10 6	66	21 2	
Diodrast 35‡	Mullen and Hughes	4–8	Yes	1000	28 4	44 3	27 3		1000	14 7	0 4
Neo Iopax 50‡	Mullen and Hughes	½	Yes	1000	24 4	44 9	30 7		1000	18 6	7 5

* Cases with allergic histories not included
† 30 cc ampules
‡ 20 cc ampules Compression used except when contraindicated

TABLE 3

Medium	Composite: Ratings: No pts	Compression	% diagnostic	% non diagnostic	Reactions: Pts	% patients one or more reactions	Roth and Nicholson: Ratings: No pts	Compression	% diagnostic	% non diagnostic	Reactions: Pts	% patients one or more reactions
Urokon 30	1100	Not reported	61 2	38 8	1100	16 8	75	No	46 7	53 3	75	10 1
Urokon 50	250	250	82 8	17 2	227	49 0	95	No	70 5	29 5	95	26 3
Urokon 70	1185	500 reported 685 not reported	77 2	22 8	870	46 2	87	No	73 5	26 5	87	39 1
Hypaque 50	1160	860	90 0	10 0	1160	9 0	97	No	71 2	28 8	97	14 5
Diodrast 35*	1000	1000	72 7	27 3	1000	14 7	66	No	57 6	42 4	66	21 2
Neo Iopax 50*	1000	1000	69 3	30 7	1000	18 6						

* 20 cc ampules for composite group and 30 cc ampules for Roth and Nicholson

TABLE 4 *Chi squared probabilities for comparison of differences of diagnostic vs nondiagnostic examinations*

	Urokon 30 3[illegible]D—40ND	Urokon 50 6[illegible]D—28ND	Urokon 70 64D—23ND	Hypaque 50 69D—28ND	Diodrast 35 [illegible]8D—28ND
Urokon 30	—	$\chi^2 = 9.92$ $p < .01$	$\chi^2 = 12.04$ $p < .001$	$\chi^2 = 10.56$ $p < .01$	$\chi^2 = 1.67$ $p < .20$
Urokon 50	$\chi^2 = 9.92$ $p < .01$	—	$\chi^2 = .027$ $p < .90$	$\chi^2 = .008$ $p < .95$	$\chi^2 = 2.93$ $p < .10$
Urokon 70	$\chi^2 = 12.04$ $p < .001$	$\chi^2 = .027$ $p < .90$	—	$\chi^2 = .136$ $p < .80$	$\chi^2 = 4.29$ $p < .05$
Hypaque 50	$\chi^2 = 10.56$ $p < .01$	$\chi^2 = .008$ $p < .95$	$\chi^2 = .136$ $p < .80$	—	$\chi^2 = 3.68$ $p < .10$
Diodrast 35	$\chi^2 = 1.67$ $p < .20$	$\chi^2 = 2.93$ $p < .10$	$\chi^2 = 4.29$ $p < .05$	$\chi^2 = 3.68$ $p < .10$	—

TABLE 5 *Comparison of diagnostic and nondiagnostic ureters*

	Medium				
	Urokon 30	Urokon 50	Urokon 70	Hypaque 50	Diodrast 35
No Patients	75	95	87	97	66
% Diagnostic	10.7	28.4	31.0	42.3	27.2
% Nondiagnostic	89.3	71.6	69.0	57.7	72.8

TABLE 6 *Chi squared probabilities for comparison of differences of diagnostic vs nondiagnostic ureters*

	Urokon 30 8D—6[illegible]ND	Urokon 50 27D—68ND	Urokon 70 27D—60ND	Hypaque 50 41D—56ND	Diodrast 35 18D—48ND
Urokon 30	—	$\chi^2 = 8.15$ $p < .01$	$\chi^2 = 9.88$ $p < .01$	$\chi^2 = 22.80$ $p < .001$	$\chi^2 = 6.40$ $p < .02$
Urokon 50	$\chi^2 = 8.15$ $p < .01$	—	$\chi^2 = .015$ $p < .90$	$\chi^2 = 4.00$ $p < .05$	$\chi^2 = .032$ $p < .90$
Urokon 70	$\chi^2 = 9.88$ $p < .01$	$\chi^2 = .015$ $p < .90$	—	$\chi^2 = 2.52$ $p < .20$	$\chi^2 = .079$ $p < .80$
Hypaque 50	$\chi^2 = 22.80$ $p < .001$	$\chi^2 = 4.00$ $p < .05$	$\chi^2 = 2.52$ $p < .20$	—	$\chi^2 = 2.40$ $p < .20$
Diodrast 35	$\chi^2 = 6.40$ $p < .02$	$\chi^2 = .032$ $p < .90$	$\chi^2 = .079$ $p < .80$	$\chi^2 = 2.40$ $p < .20$	—

TABLE 7 *Mean ratings*

Medium	Patients	Roth				Nicholson			Combined	Difference
		Visibility of			Average visibility	Opacity	Filling	Average visibility	Average visibility	Average visibility
		Calyces	Pelves	Ureters						
Urokon 30	75	1.95	1.95	1.23	1.71	2.29	2.27	2.28	2.00	.57
Urokon 50	95	2.30	2.36	1.63	2.09	2.66	2.58	2.62	2.36	.53
Urokon 70	87	2.42	2.45	1.76	2.21	2.81	2.75	2.78	2.50	.57
Hypaque 50	97	2.45	2.52	2.04	2.39	2.90	2.83	2.87	2.61	.48
Diodrast 35	66	2.06	2.09	1.70	1.95	2.37	2.48	2.42	2.19	.47

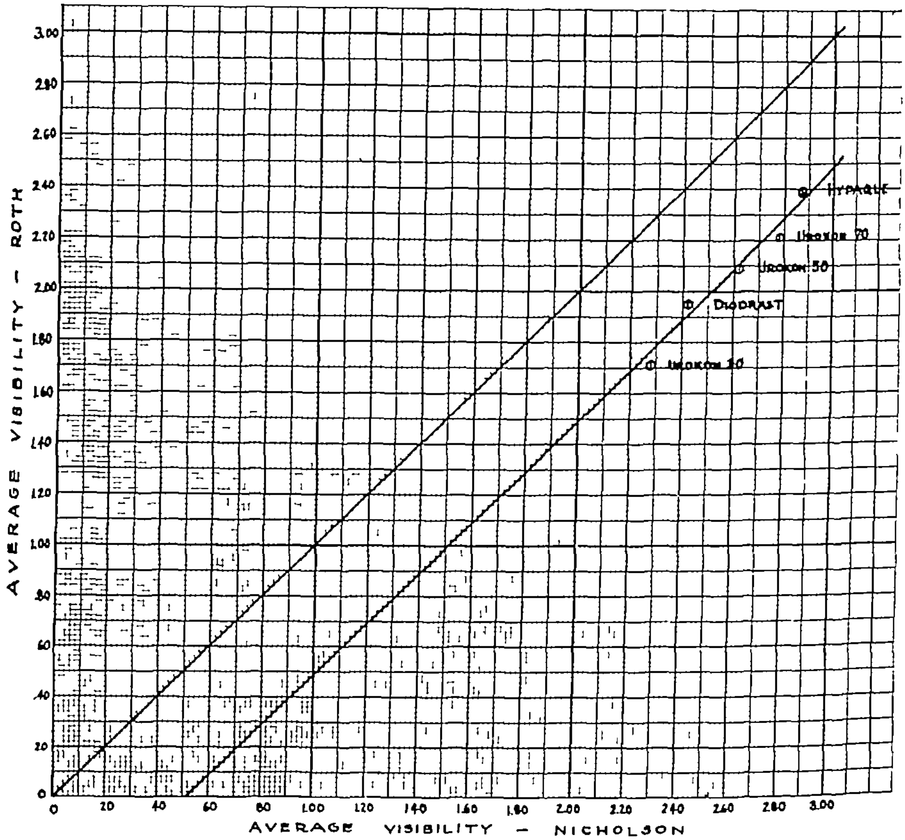


Fig 1 Comparison of the mean average visibility ratings of the two readers Note that they fall along a line parallel to a 45 degree slope with a displacement of 52 toward the abscissa Data from table 7

MECHANISM OF EXCRETION

Renal excretion is by glomerular filtration and tubular secretion About one liter of blood (25 per cent of the cardiac output at rest) flows through the kidney per minute A volume of blood equal to the total blood volume passes through the renal circulation in four or five minutes in the normal person The hydrostatic pressure of the blood is the source of energy for filtration The pressure exerted upon the glomerular capillaries is about 75 mm Hg , or approximately 70 per cent of the mean pressure in the aorta Opposing this is the osmotic pressure of the plasma proteins, about 30 mm Hg , and the renal interstitial and intratubular pressures, each about 10 mm Hg The net filtration pressure is approximately 25 mm Hg Thus, it is evident that the glomerular filtrate is dependent upon the net filtration pressure and the renal blood flow Normally, compensating adjustments maintain it at relatively constant levels Renal filtration will decline if the fall in blood pressure is too great for compensation Anuria will occur when the aortic systolic pressure falls to 70 mm Hg (about 50 mm Hg in the glomerular capillaries) Filtration will be affected by obstruction of the excretory ducts Renal edema, inflammation and glomerular or vascular disease will also impair infiltration

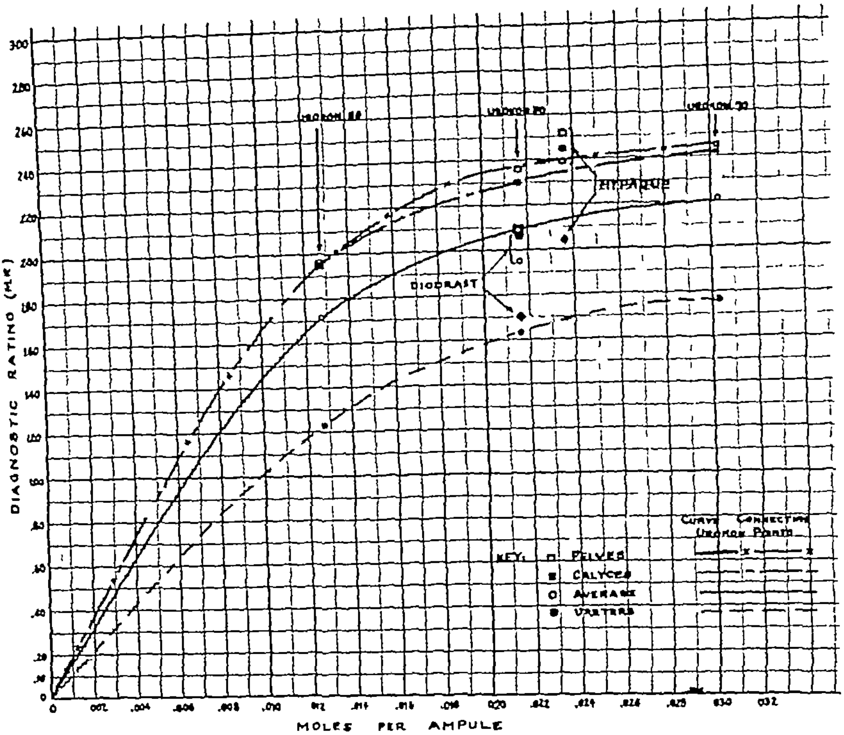


FIG 2 Plot of mean visibility ratings (M R) against molecular concentration By connecting corresponding points for urokon, a family of asymptotic curves is obtained resembling a renal excretion curve The ratings for hypaque are above the related curves for urokon and are higher than those of urokon 70 There are the same number of molecules of diodrast as there are of urokon 50, but its ratings are lower (ureters excepted) because of a lesser iodine content The ureteral rating for diodrast is slightly above the ureteral curve for urokon while that for hypaque is well above it The average visibility rating for urokon 50 is superimposed upon the pelves visibility rating for diodrast Data from tables 1 and 7

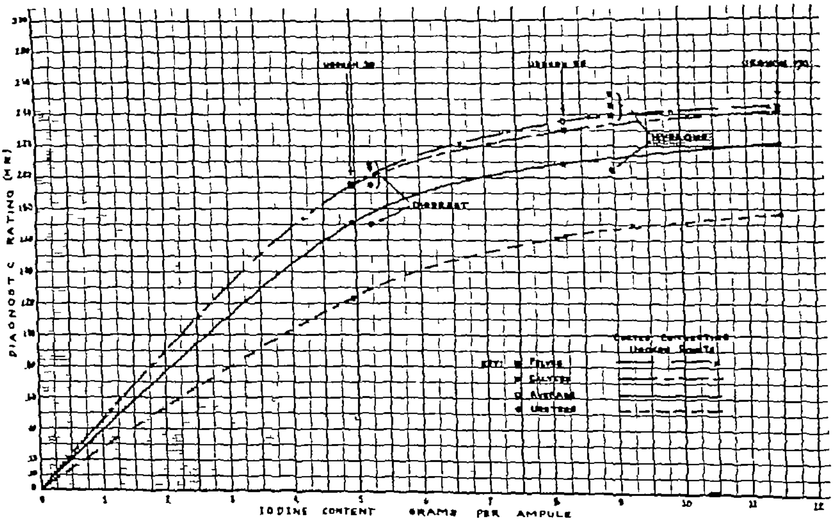


FIG 3 Plot of mean visibility ratings (M R) against iodine content Connecting similar points for urokon (as in fig 2) again produces a family of asymptotic curves The ratings for hypaque fall above these and are higher than that of urokon 70 indicating that it is a superior medium Although the molecular concentration of diodrast is the same as that of urokon 50, its iodine content is only slightly greater than that of urokon 30, hence the shift in position from that seen in fig 2 Its ratings are now above the curves for urokon Note that the ureteral ratings for both hypaque and diodrast are much higher than the ureteral curve for urokon Data from tables 1 and 7

The composition of the glomerular filtrate is determined solely by the permeability of the glomerular capillaries to the constituents of the blood The final composition of the urine is the function of the convoluted tubules by reabsorption of water and solutes In severe tubular disease, the specific gravity becomes fixed at 1 010 because of inability to do osmotic work The cells of the convoluted tubules are also capable of transporting foreign substances through them such as dyes, like phenol red, and the iodinated compounds used for intravenous urography The maximal rate at which the tubules can do this is known as the maximal tubular secretory capacity or tubular maximum (Tm)

The rate of clearance of an iodide medium increases directly with the plasma concentration until the tubular maximum is reached With larger intravenous loads, the fraction excreted by glomerular filtration rises, while that by tubular secretion falls Reports differ as to the role of tubular secretion in excretory urography Porporis et al used inulin for simultaneous excretion studies with urokon, and with para-aminohippuric acid plus urokon The low values for tubular secretion (less than 2 per cent urokon at plasma levels of 30 mg per cent or above) are probably due to the competing osmotic effects of each of the compounds within the tubular secretory mass Neuhaus et al had much higher clearance levels for tubular secretion (175–475 ml/min) with urokon alone The glomerular filtration rate was assumed to be 125 ml per minute

The maximal concentration of the organic iodide in the urine (about 0 2 molar solution) can be achieved for a short while by relatively low plasma concentrations Keates showed that the urinary iodide concentration can reach a maximum with as little as 10 cc of 35 per cent diodrast, being identical with that for 20 cc of 35 per cent and 20 cc of 70 per cent of this medium Larger quantities increased urine flow but not osmolarity which is limited by diuresis Harrow states that the x-ray density depends not only on the urine concentration but also on the amount of filling of the urinary tract structures Greater loads increase diuresis without increasing urinary tract filling, however, the urine concentration (and specific gravity) will be maintained for a longer period and pyelograms of high density should be obtained for a longer time Excessive diuresis can decrease the urine concentration with a fall of osmolarity

Increased intratubular pressure resulting from diuresis may be the reason that tubular secretion is inhibited when the plasma concentration rises above tubular maximum

Correlation of the mechanism of excretion with the data in table 7 and the graphs in figures 2 and 3 leads to the following conclusions

1 The molecular concentration of diodrast 35 and urokon 50 is the same, thus, filling of the collecting structures should be about the same because of equivalent diuresis, but the ratings for diodrast are not as good (ureters excepted) because there are only two iodine atoms in each molecule as compared to three for urokon, hence the iodine concentration in the urine is lower and the density is less Reference to table 7 shows that one of the readers (T N) rated filling higher than opacity only for diodrast

2 The iodine content for urokon 30 and diodrast 35 is nearly the same, but the ratings for diodrast are better because the molecular concentration is higher The larger number of molecules in the glomerular filtrate increases the diuresis, hence, the x-ray visibility which is dependent upon filling as well as upon iodine concentration is better

3 There is a greater increment of improvement in the ratings from urokon 30 to 50 than from urokon 50 to 70 As the molecular concentration in the urine rises, filling of the collecting structures approaches an optimum asymptotically Thus larger intravenous loads increase diuresis with little or no increase in filling

4 The iodine content and molecular concentration of hypaque are less than for urokon 70, but the ratings are above the urokon curves This may be due to local irritation of the upper tracts by urokon causing spasm, particularly of the ureters

SIDE EFFECTS

Table 8 records the side effects that were noted on the daily urogram sheets They were originally classified as mild, moderate and severe, but this is not shown on the table There were only a few severe reactions and the differences between the mild and moderate ones were not considered significant since there were several radiologists recording them

Local effects No local reactions were noted for diodrast This compares with Mullen and Hughes' series of 1000 cases where there were only 0 4 per cent with this finding Urokon 30 was next with 2 7 per cent, followed by hypaque (9 3 per cent), urokon 50 (13 7 per cent) and urokon 70 (26 4 per cent) There were about the same number of cases of leakage pain for urokon 50, urokon 70 and hypaque, but urokon 70 had the most cases of vein cramp (Root and Strittmatter) followed by urokon 50 (Keates) One case of thrombophlebitis from urokon 70 was reported the day after the patient experienced a severe vein cramp

Systemic effects Except for 1 case of mild shock from diodrast and 3 cases of urticaria from urokon 70, there were no overt hypotensive or allergic phenomena and no convulsions occurred The remainder of the systemic effects were of the vasomotor type About 10 per cent of the patients receiving urokon 30 and

TABLE 8 *Side effects*

Medium	No patients	Local Reactions					Systemic Reactions													Total Reactions			
		No patients	% patients	Vein cramp	Leakage pain	Total no local	No patients	% patients	Nausea	Vomiting	Excess salivation	Flushing	Dizziness	Palpitation	Chest pain	Urticaria	Asthma	Shock	Total no systemic	No patients	% patients	No reactions	No reactions per patient
Urokon 30	75	2	2 7	1	1	2	7	9 3	2		1	4	4						11	8	10 1	13	1 6
Urokon 50	95	13	13 7	8	8	16	19	20 0	12	5	4	5	2						28	25	26 3	44	1 8
Urokon 70	87	23	26 4	16	9	25	18	20 1	13	3	5	10	1	1		3			36	34	39 1	61	1 8
Hypaque 50	97	9	9 3	3	9	12	11	11 3	8	5	4	3							20	14	14 5	32	2 3
Diodrast 35	66	0	0			0	14	21 2	5	3	2	8	1	4	1			1	25	14	21 2	25	1 8

hypaque had one or more reactions The other media had about twice this number The average number of side effects for patients in which this occurred varied from 1 5 for urokon 50 to 2 0 for urokon 70

Total reactions Urokon 70 led the group with 39 1 per cent of patients having one or more reactions This was followed by urokon 50 with 26 3 per cent Diodrast had 21 2 per cent, hypaque 14 5 per cent, and urokon 30 had 10 1 per cent

Review of other series listed in table 2 shows wide variations for the same medium, except for hypaque which has a trend toward uniformity

Table 3 demonstrates that our findings do not compare with the composite ones except that the two media having the highest incidence of side effects are urokon 70 and urokon 50

Delayed reactions The only finding reported in followup surveys was the case of thrombophlebitis referred to above

NEWER MEDIA

Miokon 50 was added to the series in the latter stages of the study Chemically, it is similar to urokon and hypaque, except for the substitution of propionyl side chains (table 1) Its molecular weight is greater, hence for the same quantity in solution, the molecular concentration and iodine content will be correspondingly less However, the differences are relatively small and the diagnostic quality should be about the same as for hypaque It was not included in this report because it was not rotated with the other media Information to date confirms the anticipated similarity to hypaque in diagnostic quality The side effects are also about the same Ureteral filling appears to be satisfactory

We have not had any experience with renografin 76 The same theoretical considerations are applicable to it as for miokon

Hypaque 90 is currently being used in clinical research for aortography It should be an excellent medium for this provided that the side effects are not excessive If it is used for excretory urography, the increase in diagnostic quality of the films should be relatively small for the great increase in plasma concentration because of the excessive diuresis

A major contribution to excretory urography would be achieved if a compound having four iodine atoms in the molecule could be synthesized This would be a feat for the chemists who have already done an excellent job in the improvement of organic iodide media

SUMMARY

Five excretory urographic contrast media were rotated in a period of a year through 420 patients without selection The two authors used different methods in evaluating the examinations, but found that their mean values correlated consistently Hypaque had fewer side effects than urokon 50 and 70, and produced the best results, chiefly because of better filling of the ureters Presumably urokon causes ureteral spasm Comparison of visibility with molar concentration and iodine content for urokon 30, 50 and 70 results in curves resembling a renal excretion curve It appears that the tubular maximum and maximal urine concentration for urokon occurs at least by the intravenous load for urokon 30

Quantities above this increase diuresis and yield a decreasing diagnostic return Visibility is dependent upon both density (iodine concentration in the urine) and filling of the upper urinary tract structures On the basis of physical and chemical characteristics and clinical information to date, miokon should give results similar to hypaque

The principal advance to date in the preparation of iodide media has been in increasing the number of iodine atoms in the molecule from two to three Further progress will require synthesis of a compound with four iodine atoms in the molecule It will not be achieved by increasing the concentrations

The authors express their thanks to Dr Jack Blumenkrantz for consultations in statistics to Mr James Castle for drawing the graphs, to the Winthrop-Stearns, Inc , and the Mallinckrodt Chemical Works for providing media for the study

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Vol 77 No 4 April 1957
Printed in U S A

A NEW BATTERY BOX

G MADISON ROBERTS

After many years of urological practice in which I have used almost all types of batteries, I still believed that the existing batteries now in use did not meet my expectations Therefore, I submitted a design for a new battery to a friend who is an electrical engineer With his assistance we have been able to produce a battery containing many desirable features that cannot be found in any other battery on the market This is especially true in transurethral resections The battery I have designed (fig 1) is portable, weighs 10 pounds and is energized by, either or both, two long life 6 volt lantern batteries made primarily for illumination In this conjunction it contains a battery selection switch This switch is also the control switch Also contained is a potentiometer or voltage control, so that the voltage at the two main posts can be manually controlled Incorporated in this battery box are two tip jacks engraved "test" that give a fixed low voltage (approximately 2 volts) used primarily for testing instruments This source gets its voltage from the battery not in use at the main posts This selection of batteries is automatically done through the battery selector switch This feature eliminates interfering with the operating surgeon A highly accurate indicating voltmeter which has been incorporated in this box thereby gives the operator or operating surgeon visual control and avoids the burning out of many lamps

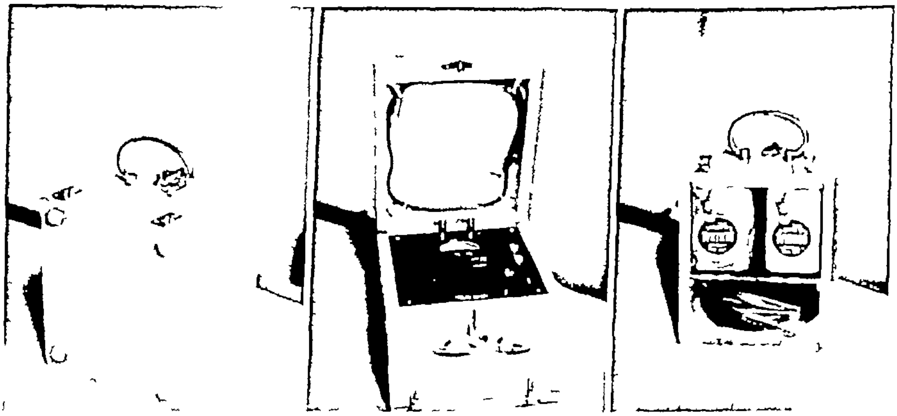
FIG 1

Should the battery in use by the operating surgeon fail, the other battery can be put in use by operating the battery selector switch

I believe another useful feature of this battery box is one of merely operating the battery selector switch to a position engraved "12", a voltage source of 12 volts can be obtained at the main posts *This voltage can be used for illuminating* low voltage head lights

Accepted for publication October 14, 1956

The expense of each battery contained is the same as the 1½ volt battery used in other units A complete change of batteries can be made without interrupting the surgeon with the ease used in changing the batteries in a flashlight Also provided is a place in the box to carry an extra cord and lamps

It is my opinion that this meets a long felt want for illumination in small electrical instruments

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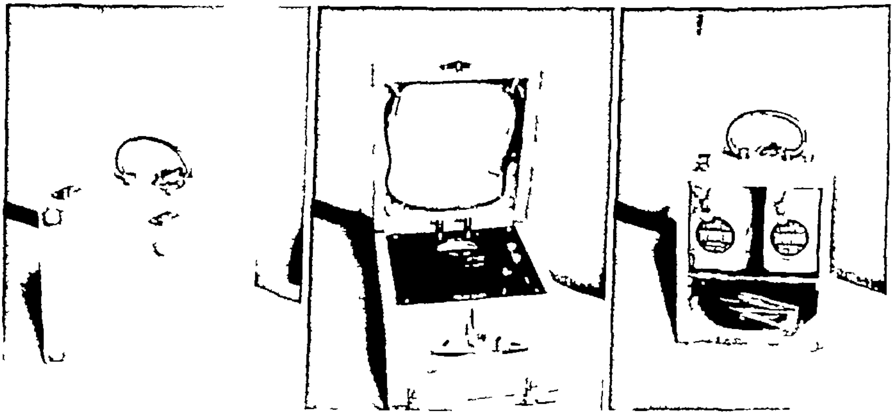

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Mid Atlantic—Hotel Jefferson, Richmond, Va, October 1–4, 1958
Northeastern—White Face Inn, White Face, N Y September 8–11, 1957
North Central—Grand Hotel, Mackinac Island, Mich August 28–30, 1957
Southeastern—Atlanta, Ga April 7–11, 1957
Western—Olympic Hotel, Seattle, Wash May 27–30, 1957
South Central—Oklahoma City, Okla, October 21–24, 1957

Note by editor A complete list of the executive committees of the various sections, and a complete list of the officers and members of the executive committees of the various branch societies will be printed in the December 1957 issue

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INFLUENCE OF URINARY GLUCURONIDE ON SOLUBILITY OF CALCIUM PHOSPHATE AND STONE FORMATION. EXPERIMENTAL UROLITHIASIS XII

C. W. VERMEULEN, B. FINLAYSON AND W. CHAPMAN

From the Department of Surgery, University of Chicago, Chicago, Ill.

Prien and Walker[1, 2] have reported that formation of urinary calculi of the calcium phosphate type seems to be impeded when patients are treated with aspirin or salicylamide. Salicylate therapy was conceived by them as a simple and effective means for increasing the urinary glucuronide excretion which in turn would increase the solubility of the calcium salts in the urine.

The ability of conjugated glucuronides to solubilize calcium salts was first reported by Neuberg and Grauer.[3] They studied a number of other organic substances for their ability to increase the solubility of relatively insoluble salts. Our chief concern is with their observations on solubilizing by glucuronides for which they used the ammonium salt of menthol glucuronide prepared from the urine of rabbits. A typical experiment as reported by them is as follows: To 0.3 ml. of 0.1 molar calcium chloride solution 0.3 ml. of a 0.1 molar disodium hydrogen phosphate solution was added. A precipitate of calcium phosphate occurred. If, however, the same amounts of the same solutions were added to 3 ml. of menthol glucuronide solution, no precipitation occurred. The glucuronide solubilized the calcium phosphate. It is important to note that a very high concentration of menthol glucuronide was used—a M/8 solution containing approximately 46 grams per liter.

Prien and Walker, in addition to their clinical observations, have reported some in vitro tests using both a crude salicyl glucuronide mixture isolated from human urine and a synthetic salicyl glucuronide. A 1 per cent solution of the crude material increased the solubility of calcium phosphate by 30 to 40 per cent. The synthetic glucuronide yielded increases in solubility of 8.7 and 16 per cent with solutions of 0.05 and 0.1 per cent concentrations.

In this paper it is our purpose to report on three types of experiment bearing upon the fascinating treatment recommended by Prien and Walker. The first experiment is concerned with stone inhibition in the rat. The second deals with the ability of menthol glucuronide (the original substance employed by Neuberg

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and Grauer) to solubilize calcium salts The third experiment was done to see if salicylamide therapy had any detectable effect upon the solubility of calcium phosphate in the urine of 2 normal male subjects

RAT EXPERIMENTS

Methods In the rat experiments the same general techniques were employed as in previous publications of this series[4] It has been shown that stones of 2 different chemical types are formed dependent upon the type of rat used[5] Adult male rats obtained from the Harlan Animal Farm were used to produce stones of the magnesium ammonium phosphate type, and adult females from the Holtzman Rat Company to form stones of the calcium phosphate variety As in previous experiments, standard discs of sheet zinc were inserted surgically into the bladder to serve as foreign bodies to stimulate stone formation A normal non calculogenic diet was given consisting of Purina Laboratory Chow Water was available at all times

Two different medications, aspirin and isoborneol, were given to increase the glucuronide excretion Isoborneol was used after it was discovered that aspirin does not greatly increase the urinary glucuronide excretion in the rat Isoborneol, a chemical relative of menthol, on the other hand, is known to produce a marked increase in glucuronide output in rats[6] The drugs were mixed with the food, treatment being continued from the time the foreign body was implanted until the termination of the experiment The dosages as described in this paper are given in milligrams of drug per 100 grams of food For our rats a concentration of drug of 35 mg per cent in the food results in an approximate dose of 35 mg of drug per kilogram of rat (For comparison, a human dose of 2 gm per day equals approximately 30 milligrams per kilogram per day for a man weighing 70 kilograms) There seemed to be no evidence of toxicity with the dosages and medications employed

Quantitative collections of urine for chemical analysis were done by methods previously reported in this series[4] Urinary glucuronide determinations were done by the method of Dische[7]

All experiments were of 6 weeks' duration The animals were then operated upon and urine aspirated from the bladder for pH determination and bacteriologic culture The bladder was now opened and the stone or foreign body removed In order to avoid confusion due to the effects of intercurrent infection,[8] only those animals are included in this report in which the urine was proved to

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TABLE 1 *Influence of aspirin and isoborneol on stone growth in rats with bladder foreign bodies*

Type of rat used	Treatment	Number of rats	Average pH of urine	Average weight of stone in mg
Harlan Male ("magnesium" stones)	Control	36	6 6	48 1
	Aspirin—35 mg %	10	6 5	70 9
	Aspirin—100 mg %	24	6 3	44 1
	Isoborneol—600 mg %	16	6 3	50 2
Holtzman Female ("calcium" stones)	Control	31	6 7	48 4
	Aspirin—100 mg %	17	6 4	40 6
	Aspirin—300 mg %	8	6 4	57 2
	Isoborneol—600 mg %	20	—	76 0

Duration of experiment 6 weeks Harlan male rats produce stones composed of magnesium ammonium phosphate while Holtzman females usually produce calcium phosphate stones Indicated aspirin dosage is the concentration in the powdered food

be sterile on culture The amount of stone produced in any rat was determined by weighing the stone and subtracting the initial weight of the foreign body Not all the rats reported in this paper were run simultaneously since the isoborneol experiment was done later than the aspirin study However, each group was accompanied by a simultaneous control group Since no significant difference was found in groups run at different times, the results on average stone growth have been lumped together in the summarizing table and graph

Results Feeding of either aspirin or isoborneol was without effect on the amount of stone formed in either Harlan male rats (which produce "magnesium" stones) or Holtzman female rats (which produce "calcium" stones) Details of the different groups are given in table 1 and graphically presented (fig 1) Quantitative analysis of the stones produced in the Harlan animals was not done but previous experience with analyses of several hundred calculi formed in such animals has almost invariably indicated that they are nearly pure magnesium ammonium phosphate As a check of the type of stone formed in the Holtzman females, the first five stones produced in each of the 4 groups were quantitatively analyzed Of the 20 stones studied, only 2 contained less than 15 per cent calcium The average for the 20 stones was 20 9 per cent as calcium, thus confirming our previous observation that this type of animal produces a stone composed primarily of calcium phosphate

Tables 2 and 3 give representative results of the urine examinations No significant difference was found in the concentration of calcium, magnesium, or phosphorus in the animals receiving aspirin Though aspirin increased the glucuronide excretion to some degree, the increase was not great On the other hand, isoborneol increased the urinary glucuronide level to more than 4 times the control figure

Discussion As already mentioned, neither aspirin nor isoborneol was capable of impeding stone formation in these experiments The slight differences in the average amount of stone produced in the experimental and control groups are

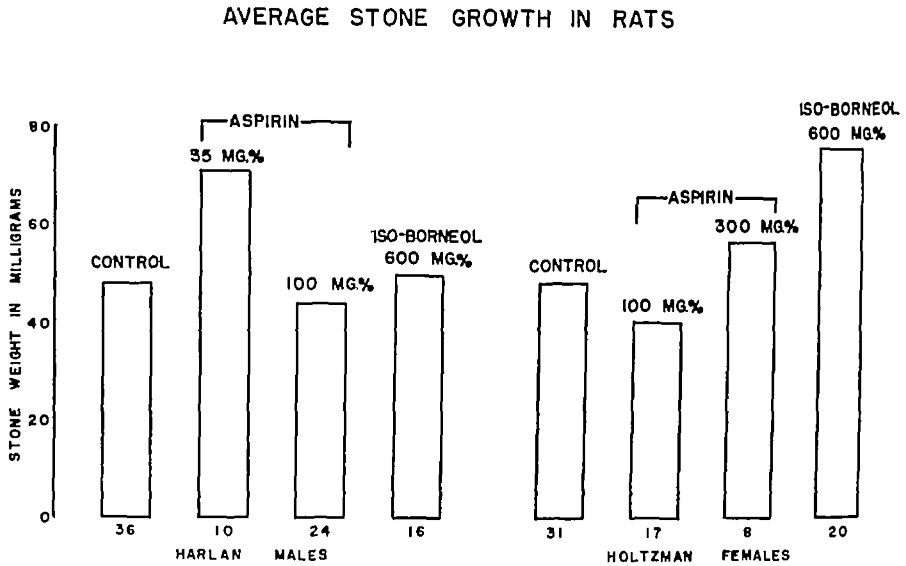

FIG 1 Graph showing average weight of "magnesium" stones (Harlan males) or "calcium" stones (Holtzman females) produced in rats without treatment or treated with aspirin or isoborneol Dosage, above bars, given in mg % of the food Number below each bar indicates number of rats in group Duration of experiment, 6 weeks

without significance and doubtless due to chance variation The results therefore do not support the concept of Prien and Walker

In considering experiments using the foreign body technique the question may be asked Are results of such experiments of any validity in connection with the human disease? Admittedly urolithiasis is not a disease in which stones are usually formed upon foreign bodies though the role of nuclei in the genesis of stones is by no means resolved Yet our experience with rat foreign body stones leads us to believe that in many respects they are remarkably similar to human calculi Both in structure and chemical composition there is a close relationship It may be of interest to add that recent examinations have shown that they contain a muco-protein matrix material similar to that described by Boyce and Garvey[9] in human calculi As a further similarity it has been shown that many factors thought to bear upon the human disease have affected rat stone formation of this type[4 8 10 11] Moreover, the method lends itself nicely to quantitation and critical evaluation The foreign body technique is particularly apt as a tool for investigation of salicylate therapy since one of the evidences used to support this therapy is the prevention of catheter encrustation which is also a kind of foreign body calculus disease

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[9] Boyce, W H and Garvey, F K The amount and nature of the organic matrix in renal calculi J Urol , 76 213-227, 1956

[10] Grove, W J , et al Experimental urolithiasis II Influence of urine volume upon calculi experimentally produced upon foreign bodies J Urol , 64 549, 1950

[11] Vermeulen, C W , et al Experimental urolithiasis IV Prevention of magnesium ammonium phosphate calculi by reducing the magnesium intake or by feeding an aluminum gel J Urol , 66 6, 1951

TABLE 2 *Urine chemistry Harlan male rats*

Treatment	Number of rat days studied	Aver food intake	Urine averages		
			Volume	Calcium	Phosphorus
		grams/day	ml.	mg %	mg %
Controls	20	20.3	14	7.14	101
Aspirin 35 mg %	20	20.5	14	5.84	105
Aspirin 100 mg %	17	16.9	11.5	6.9	100

TABLE 3 *Glucuronide excretion Holtzman female rats*

Treatment	Number of rat days studied	Average urine volume	Glucuronide excretion
		ml./day	mg./day
Control	17	12.6	11.4
Aspirin 100 mg %	18	13.9	14.5
Aspirin 300 mg %	16	16.7	14.6
Control	11	11.7	8.1
Isoborneol 600 mg %	11	12.4	35.4

Our failure to demonstrate stone impedence with aspirin is not surprising if salicylates act by way of increasing the concentration of conjugated glucuronides in the urine We found, as reported earlier by Smith,[12] that feeding of aspirin to rats does not greatly increase the urinary glucuronides In the rat detoxication of salicylate is apparently not accomplished in the same manner as in man However, subsequent parts of this paper seem to cast doubt on the effectiveness of glucuronides as solubilizers in stone disease If another mechanism be called upon to support salicylate therapy (such as the "anti-rheumatic" effect suggested by Baker and Connelly,[13]) then our rats also failed to demonstrate such an aspirin mechanism Rats fed isoborneol gave a good glucuronide response but this medication again failed to impede stone growth If increased urinary glucuronide increases the solubility of the stone-forming salts, then its action is not sufficiently powerful to be detectable by the foreign body technique used

One may not conclude from a negative experiment of this type that salicylate therapy is of no value It is possible that the salicylates act in some way yet unknown which would not be applicable to the rat, or more particularly to the rat when a foreign body is used to initiate stone formation If the results had been positive and shown an effect, they would have been strong support for this type of therapy but negative experiments are never as forceful in clinical implication

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[12] Smith M J H Some recent advances in pharmacology of salicylates J Pharm and Pharmacol 5 81, 1953

[13] Baker R and Connelly, J P Bilateral and recurrent renal calculi Evidence indicating renal collagen abnormality and results of salicylate therapy J.A.M.A., 160 1106, 1956

SOLUBILIZING BY MENTHOL GLUCURONIDE

Methods The original glucuronide used by Neuberg and Grauer was menthol glucuronide We thought it worthwhile to extend their observations using the same material but with quantitative techniques and at various glucuronide concentrations It will be remembered that the concentration used by them amounted to about 46 grams per liter, far beyond physiologic levels Ammonium menthol glucuronide is commercially available in a pure crystalline form Solutions of it were made in distilled water at concentrations of 0 2, 0 5, 1 0, and 3 0 per cent One ml of a 0 1 molar calcium chloride solution was added to 10 ml of each glucuronide solution in a glass-stoppered tube After mixing, 1 ml of a 0 1 molar disodium hydrogen phosphate solution was added and the tubes again mixed A control tube containing 10 ml of distilled water was treated similarly The five tubes were shaken on a mechanical shaker for exactly 1 hour After centrifuging for 5 minutes, the supernatant was filtered through paper The pH of the filtrate was obtained (glass electrode), and analysis for calcium and phosphorus carried out This test was performed on 4 successive days A similar study was made with solutions of the glucuronide in normal urine instead of distilled water

A test was also done to determine if glucuronide produced some kind of calcium complex by using a method previously reported[14] in which it was shown that impedence of calcium dialysis occurs in the presence of a calcium complexing agent A 1 per cent solution of menthol glucuronide containing approximately 23 mg per cent calcium was dialysed against water at a pH of 6 5 for 2 hours on the rapid dialysis machine A simultaneous dialysis was done using citrate instead of glucuronide and a control in which no complexing agent was present

Results Using the filtrate calcium levels as an index of the calcium phosphate solubility, figure 2 gives the averaged results of the experiment testing the solubilizing power of menthol glucuronide in water Whereas the control averaged 8 9 mg per cent calcium, the level increased to 11 3 mg per cent in the presence of 1 per cent glucuronide and to 15 mg per cent in the tubes of highest, or 3 per cent concentration Corresponding increases in phosphorus also occurred The pH in all tubes was remarkably constant with an average that varied from 6 15 to 6 22 in the 5 sets of tubes With such slight variations the differences in solubility cannot be attributed to pH effect When the glucuronide concentration was 1 per cent or above, distinct solubilizing thus occurred, but very little action was demonstrated at lower concentrations When similar tests were done with urine instead of water, similar results were obtained It should be mentioned that the concentration of glucuronide used originally by Neuberg and Grauer was somewhat higher than the highest concentration used in the present experiment

The results of the dialysis experiment may be seen in table 4 Approximately 20 per cent of the calcium remained undialysed in the presence of 1 per cent menthol glucuronide At the same time a tube containing 0 1 per cent citrate showed a similar amount of undialysed calcium The third, or control tube, con-

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[14] Vermeulen, C W , et al Experimental urolithiasis X On the state of calcium in the urine J Urol , 76 592, 1956

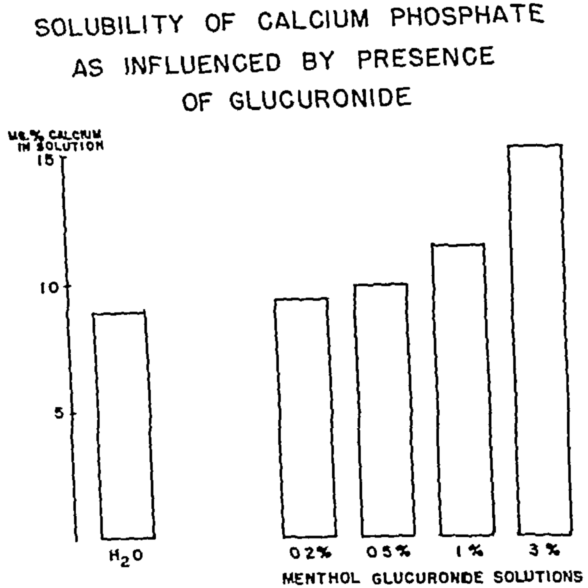

Fig 2 Graph showing average solubility of calcium phosphate in solutions of menthol glucuronide at different concentrations Solubility in water also given as control

Table 4 *Menthol glucuronide a calcium "complexer" as determined by rapid dialysis*

	Initial Calcium mg %	Final Calcium mg %
H O* control	23 2	trace
Citrate 100 mg %	23 5	5 1
Menthol glucuronide 1 gm %	22 9	5 5

Water solutions, all containing calcium, dialyzed against distilled water at pH 6 5 for 2 hours

taining neither citrate nor glucuronide, gave complete dialysis Thus 1 per cent glucuronide was about as effective as 0 1 per cent citrate solution in impeding calcium dialysis

Discussion The solubility tests are significant, we believe, in that menthol glucuronide was the material with which the solubilizing properties of the conjugated glucuronides were first described by Neuberg and Grauer We at first prepared menthol glucuronide from the urine of rabbits fed menthol just as Neuberg and Grauer had done but found that our material, when dissolved in water, altered the pH to such an extent as to be out of the physiologic range Pure menthol glucuronide was then obtained commercially and the composition of the material confirmed by chemical analysis We found that in concentration similar to that used by Neuberg and Grauer, its solubilizing power was easily detectable though not striking in magnitude These high concentrations, of course, are far beyond those attainable physiologically At lower concentrations less and less solubilization occurred At a concentration roughly equivalent to what one might expect with salicylate therapy the power of increasing solubility could not be detected by the methods used The result, then, indicates that if salicylate in stone disease works by way of the glucuronide mechanism, the salicyl glucuronide is very much more powerful than menthol glucuronide from which the whole concept sprang

The test employed here in studying solubility is by no means thoroughly understood The precipitate formed when phosphate ions are added to a solution containing calcium ions varies in composition dependent upon several factors, the most important of which is probably the hydrogen ion concentration It is not our purpose here to engage in a discussion of this subject since we hope in a future paper to consider this test in further detail While the validity of the test might then be uncertain in relation to stone disease, it was, nonetheless, the very test used by Neuberg and Grauer that gave rise to the whole salicylate concept

The mechanism of solubilizing by glucuronide has been thought to be by complexing or perhaps chelating with calcium thus reducing the effective concentration of the calcium ion The dialysis experiment suggests that some sort of complexing does indeed occur The simultaneous study with citrate is helpful in indicating the relative strength of those two substances as calcium binders The glucuronide was roughly about one-tenth as strong as the citrate The mechanism for calcium binding, whether simple complexing, chelating, or some other type of binding cannot be determined from this study

HUMAN EXPERIMENT

Methods Our purpose here was to determine if administration of salicylamide results in a detectable difference in the solubility of calcium phosphate in the urine Two normal male subjects (V J aged 17, and V S aged 44) were on an unrestricted diet and water intake for the duration of the experiment lasting 4 weeks During this time, salicylamide was given for periods of 2 days alternating with periods without treatment of 2 or 3 days' duration During the treatment periods 2 gm of salicylamide were given daily in divided doses Observations are available from 6 treatment and 6 control periods with each subject

A total of 20 urines from each subject were studied for solubility during the investigation, half while on treatment and half while off treatment These specimens consisted of single voidings obtained upon arising from sleep The experiment was arranged so that most of the specimens were collected at the end of the treatment or control periods

On each specimen the calcium and phosphorus content was determined as well as the specific gravity and pH For study of the calcium phosphate solubility two different methods were used The first method was the same as that described in the previous section on menthol glucuronide solubilizing, using 1 ml each of 0 1 molar calcium chloride and disodium hydrogen phosphate solutions to 10 ml of urine The tubes were shaken for 1 hour, centrifuged for 5 minutes, and filtered The pH, calcium, and phosphorus were determined on the filtrate This test we have labeled the "precipitation test"

The second test attempts to approach the saturation point from the opposite

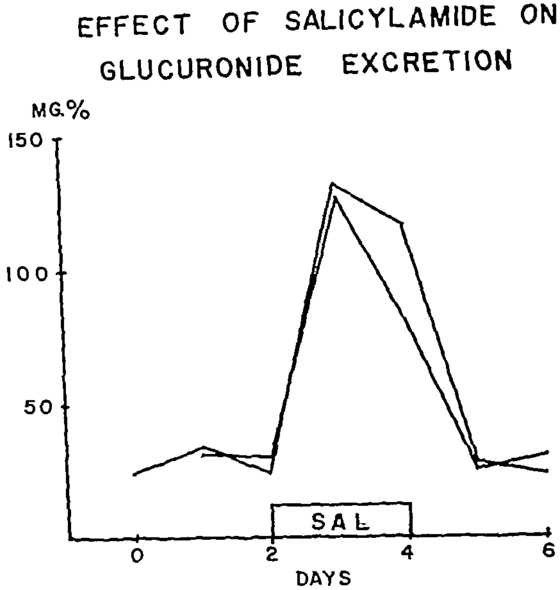

FIG 3 Graph showing glucuronide concentrations (expressed as glucurono lactone) in urine with effect of administration of 2 gm /day of salicylamide for 2 days Prompt rise and fall are demonstrated coincident with treatment

TABLE 5 *Intermittent administration of salicylamide averages of control and treatment periods*

	Number of tests	Urine volume	ine pH	Urine calcium	Solubility by precipitation test
		ml		mg %	Ca mg %
Experiment on N J					
Control	10	399	5 48	13 7	41 8
Salicylamide	9	442	5 55	11 4	35 6
Experiment on V S					
Control	9	515	5 85	7 0	30 4
Salicylamide	10	531	6 06	4 2	20 6

direction Essentially it is a modification of the test described by Flocks[15] in which urine was shaken with solid calcium phosphate This test has also been recently used by Andrews et al [16] The solid material we used was actually a powder obtained by grinding up a single large human bladder stone that on analysis was composed of 22 per cent calcium and 14 6 per cent phosphorus In performing the the test 10 ml of urine were shaken for 1 hour on a mechanical shaker with 30 mg of the stone salt The pH, calcium, and phosphorus in the filtrate were determined after shaking We have called this test the "stone salt test " what one might expect with salicylate therapy the power of increasing solubility could not be detected by the methods used The result, then, indicates that if salicylate in stone disease works by way of the glucuronide mechanism, the salicyl glucuronide is very much more powerful than menthol glucuronide from which the whole concept sprang

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[15] Flocks, R H Prophylaxis and medical management of calcium urolithiasis the role of the quantity and precipitability of the urinary calcium J Urol , 44 183, 1940

[16] Andrews, J C , Yarbro C L , Golby, R L and Sell, I T Studies on the mechanism of formation of renal calculi, I J Urol , 73 930, 1955

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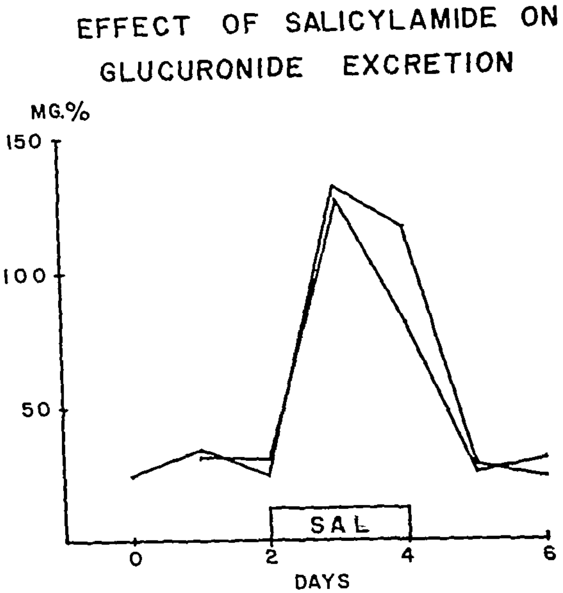

Fig. 3. Graph showing glucuronide concentrations (expressed as glucurono lactone) in urine with effect of administration of 2 gm./day of salicylamide for 2 days. Prompt rise and fall are demonstrated coincident with treatment.

Table 5. *Intermittent administration of salicylamide averages of control and treatment periods*

	Number of tests	Urine volume	Urine pH	Urine calcium	Solubility by precipitation test
		ml.		mg %	Ca mg %
Experiment on V. J.					
Control	10	399	5.48	13.7	41.8
Salicylamide	9	442	5.55	11.4	35.6
Experiment on V. S.					
Control	9	515	5.85	7.0	30.4
Salicylamide	10	531	6.06	4.2	20.6

direction. Essentially it is a modification of the test described by Flocks[15] in which urine was shaken with solid calcium phosphate. This test has also been recently used by Andrews et al.[16] The solid material we used was actually a powder obtained by grinding up a single large human bladder stone that on analysis was composed of 22 per cent calcium and 14.6 per cent phosphorus. In performing the the test 10 ml. of urine were shaken for 1 hour on a mechanical shaker with 30 mg. of the stone salt. The pH, calcium, and phosphorus in the filtrate were determined after shaking. We have called this test the "stone salt test."

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[15] Flocks, R. H.: Prophylaxis and medical management of calcium urolithiasis: the role of the quantity and precipitability of the urinary calcium. J. Urol., 44: 183, 1940.

[16] Andrews, J. C., Yarbro, C. L., Golby, R. L. and Sell, I. T.: Studies on the mechanism of formation of renal calculi, I. J. Urol. 73: 930, 1955.

Glucuronide determinations were done as an additional experiment to see if proper responses to salicylamide were being obtained Again the method of Dische was used for these estimations

Results With both experimental subjects good elevations in urinary glucuronide were obtained on salicylamide As shown in figure 3, the glucuronide con-

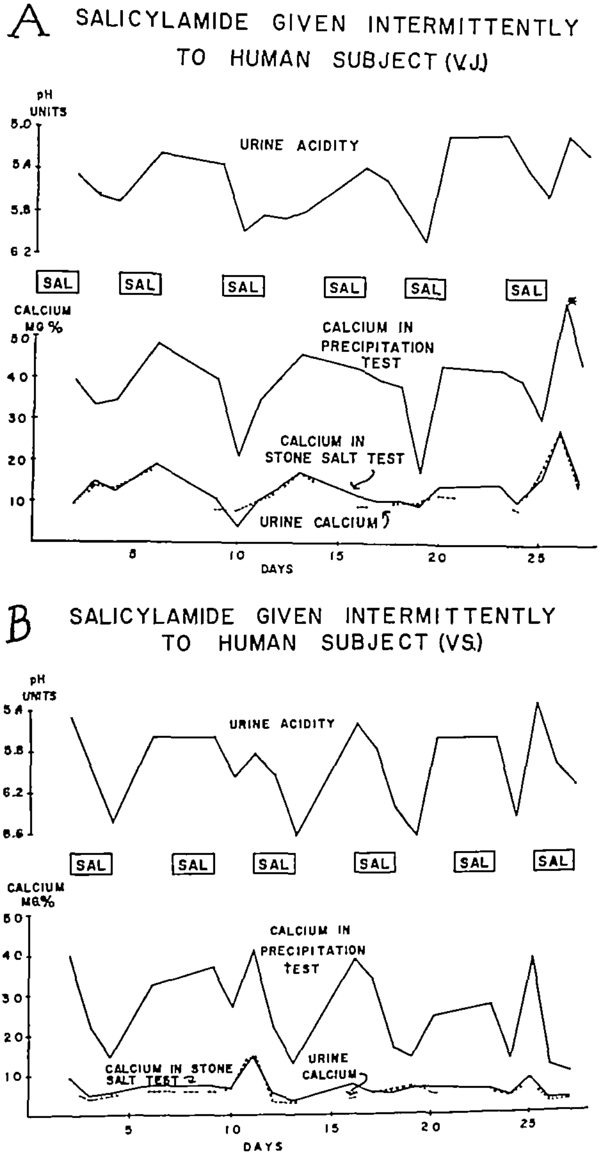

Fig 4 *A*, graph of experiment where salicylamide was given intermittently to V J showing no effect of treatment on solubility by "precipitation test" or "stone salt test" *, No precipitate occurred at this point, under conditions of test, this particular sample was therefore "unsaturated"

B, graph of experiment where salicylamide was given intermittently to V S showing no effect of treatment on solubility

TABLE 6. *Selecting pairs of specimens with comparable pH* and averaging the results*

	Urine pH	Urine calcium	Solubility by precipitation test
		mg %	Ca mg %
Experiment on V. J.			
6 control tests	5.41	11.9	40.5
6 salicylamide tests	5.42	12.6	40.0
Experiment on V. S.			
6 control tests	6.02	7.3	27.3
6 salicylamide tests	6.03	4.5	24.3

* To eliminate from this experiment the effect of pH on solubility, pairs of specimens were selected from the control and treatment periods having almost identical pH (range 0.05 pH units). Six such pairs were possible in each of the 2 test subjects.

tent of the urine rose promptly on administration of the drug and fell rapidly after its cessation.

Table 5 summarizes the other results obtained. In the periods when salicylamide was being given, the average urine volume, pH, and urine calcium levels differed somewhat from the control periods. Whether these changes are due to the drug is doubted, since no attempt was made to rigidly control any of these factors. When the solubility studies were averaged, it was found that no increase in solubility could be detected in the periods while receiving treatment. The test of solubility in which the urine was shaken with stone salt is omitted from the table since the variations were not as significant as those found with the *precipitation test*.

From the graphs (fig. 4) it is strikingly evident that the solubility by the precipitation test is closely related to the pH of the urine specimens, the more acid the urine the greater the solubility. The stone salt test gave results in which the filtrate calcium usually corresponded closely with the original urine calcium. The fluctuations found with the precipitation test were much more marked and almost always in relation to the urinary pH. Phosphorus determinations, though done in all these studies, are not described. They paralleled the calcium changes but in a less striking manner. It is interesting to note that the solubility by the precipitation test is always much higher than that of the stone salt test.

From figure 4 it is quite evident that pH plays a very important role in determining the amount of calcium that will remain in solution by the *precipitation test*. But since the pH varied considerably from day to day, a benefit from salicylate could be masked by adverse pH changes. The results were therefore analyzed by pairing all possible data from the control and treatment periods in which the pH of the specimens were identical or almost so (within a range of 0.05 pH units). Six such pairs could be made for each experimental subject as shown in table 6. Here, of course, the averages of the pH in the control and salicylamide periods are practically identical so that pH influence is eliminated. With one subject the urine calcium averaged slightly higher on salicylamide while with the other subject the reverse occurred. The important figures are on the solubility as determined by the *precipitation test*. There was essentially no difference between the averages on salicylamide and those when no treatment was being given

Discussion This experiment attempted a more direct attack on the question Does salicylate increase the solubility of calcium phosphate in the urine? It was hoped that by alternating treatment and control periods the other variables that influence solubility would average themselves out We were only partly successful in this regard We believe, however, that any significant effect of salicylamide therapy would have become evident

Of the two tests for solubility used, the precipitation test seemed to give much more useful information With both tests we found that the calcium determinations in the filtrate were more useful than the phosphate though much more laborious This is in part due to the fact that urinary phosphorus is already proportionately much higher than the calcium and therefore the changes are much less marked

The most striking alteration in solubility was found due to differences in pH This serves to substantiate the validity of the test since the influence of pH on calcium phosphate solubility is well known But at the same time uncontrolled variations in pH might possibly mask an effect by salicylate The technique of pairing was therefore resorted to in which the pH of the members of each pair was identical When this was done, no benefit from salicylamide could be detected

SUMMARY

Neuberg and Grauer, using menthol glucuronide as the test material, reported that the presence of glucuronides increases the solubility of calcium phosphate Using this finding, Prien and Walker have suggested that salicylate administration may be beneficial in patients with urolithiasis since salicylate is excreted in part as conjugated glucuronides The experiments here reported were done to see if confirmation of this concept could be obtained

In the first experiment rats with foreign bodies in the bladder were used to stimulate stone formation Feeding of aspirin failed to inhibit stone growth, but it was found that rats do not excrete significant amounts of administered salicylate as conjugated glucuronides Therefore, isoborneol, a known augmenter of glucuronide excretion was tried Again no impedence of stone formation occurred

In the second experiment the original observations of Neuberg and Grauer on menthol glucuronide solubilizing were extended to include concentrations at more physiological levels While their original observation with high concentrations could be confirmed, the solubilizing power of this material was barely detectable at glucuronide concentrations comparable to those that could be expected from salicylate administration

In the third experiment salicylamide was intermittently administered to 2 normal human subjects The urine was studied for calcium phosphate solubility by two different methods No difference was found between the urines obtained during treatment and those obtained in the intervals between treatment

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RENAL ARTERY ANEURYSM: REPORT OF 12 CASES, TWO TREATED BY EXCISION OF THE ANEURYSM AND REPAIR OF RENAL ARTERY

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Aneurysm was the first disease of the renal artery to be recognized, but there are comparatively few reports of its occurrence. The frequency of renal artery aneurysm at autopsy has been estimated as 1 in 11,100 (0.01 per cent) cases[1] but it is unlikely that this represents the true incidence of the disease because small aneurysms are not readily recognized at autopsy. Abeshouse[2] in 1951, reported that 115 cases, including two of his own, had been recorded. Since then, 14 more cases have been reported,[1, 3-12] bringing the total to 129. It is the purpose of this paper to present the findings in additional 12 cases that have been seen since 1952.

Aortography now provides the urologist with an accurate means of diagnosis of renal artery aneurysm and, with modern techniques of arterial surgery, it is probable that many more cases will be recognized and treated successfully. However, no matter how rare the disease, if it is curable it is important to recognize it.

Read at annual meeting, North Central Section of American Urological Association, Cleveland, Ohio, October 3-5, 1956.

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PATHOLOGIC FINDINGS

Of the 12 patients in this series, seven had saccular aneurysms (one had multiple saccular microaneurysms associated with partial stenosis of the renal artery), three had poststenotic or jet aneurysms, one had a noncalcified fusiform aneurysm, and one had an arteriovenous aneurysm

The type of aneurysm most frequently found in the renal artery is the *saccular aneurysm* (fig 1, *A*) This is a true aneurysm because its wall is made up of one or more coats of the renal artery It is a localized dilatation or pouching that may occur anywhere along the renal artery, but it is often found at a point of bifurcation It is generally accepted that these aneurysms result from congenital defects in the elastic tissue of the medial coat of the artery at the point of bifurcation They usually are from 1 to 4 cm in diameter, but may be larger The aneurysm eventually undergoes extensive arteriosclerosis and becomes calcified, producing the typical opaque, ringlike shadow near the hilum of the kidney on plain roentgenograms of the abdomen (fig 2, *A*) Inflammatory lesions of the renal artery are an infrequent cause of aneurysm [2]

Seven of the 12 patients in this series had saccular aneurysms, all but one were calcified One of these seven patients had aneurysms of both renal arteries and also multiple aneurysms of the splenic artery (fig 2, *A* and *B*) Two other patients each had a saccular aneurysm of the left renal artery associated with a similar aneurysm of the splenic artery (fig 3) Three patients each had a single large aneurysm of the renal artery The seventh patient, a 30-year-old woman with benign hypertension of three years' duration, had multiple noncalcified saccular microaneurysms associated with partial stenosis of the renal artery and two of its branches In this patient it is believed that degenerative changes of the elastic tissue and media were important in the pathogenesis of the microaneurysms

An unusual type of aneurysm known as a *poststenotic* or *jet aneurysm*[13] results from partial obstruction of the renal artery by an arteriosclerotic plaque (fig 1, *C*) It is similar to the jet aneurysm that often is found just distal to the coarcted segment of thoracic aorta [14] It is believed that the arteriosclerotic plaque causes stenotic blood flow and deflects a jet stream of blood against the arterial wall The artery is thereby weakened, and degenerative changes occur in the media of the blood vessel, asymmetrical dilatation, in the larger aneurysms, occurs and may involve a considerable length of the renal artery (fig 4) During the past 4 years, many hypertensive patients have been studied by aortography and three have been found to have this type of lesion of the renal artery A number of other hypertensive patients with renal artery stenosis have shown a symmetrical but smaller poststenotic dilatation

Of the remaining 2 patients, one had a large *noncalcified fusiform aneurysm* of the renal artery occurring at the renal hilus in association with an extensive

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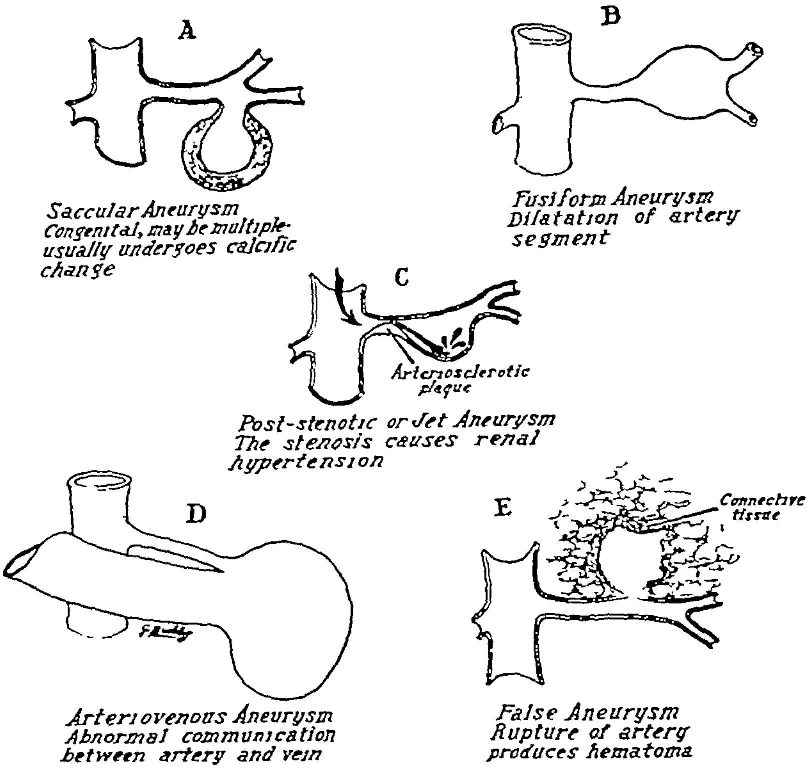

FIG 1 Diagrams of various types of renal artery aneurysms

hypernephroma (fig 1, *B*) In this instance the artery was dilated to form an aneurysm approximately 3 by 1½ cm This dilatation is another type of true aneurysm and is differentiated from the saccular aneurysm because a segment of the artery is involved in the dilatation It is probable that in this patient the increased blood demands of the tumor were important in the pathogenesis of the aneurysm

The twelfth patient in this series had a large *arteriovenous aneurysm* at the point of ligature of the renal pedicle after nephrectomy (fig 1, *D*) This type of aneurysm is an abnormal communication between the artery and vein and probably arises from simultaneous laceration of the adjoining vessels (fig 5)

A *false aneurysm* of the renal artery is defined as an aneurysm whose wall is made up of tissues originating outside the renal artery (fig 1, *E*) It actually is a hematoma with arterial communication and results from spontaneous or traumatic rupture of the artery

SYMPTOMS AND SIGNS

Only two of the 7 patients with saccular aneurysm of the renal artery had symptoms referable to the aneurysm These 2 patients had intermittent upper abdominal pain The patient with multiple noncalcified microaneurysms associated

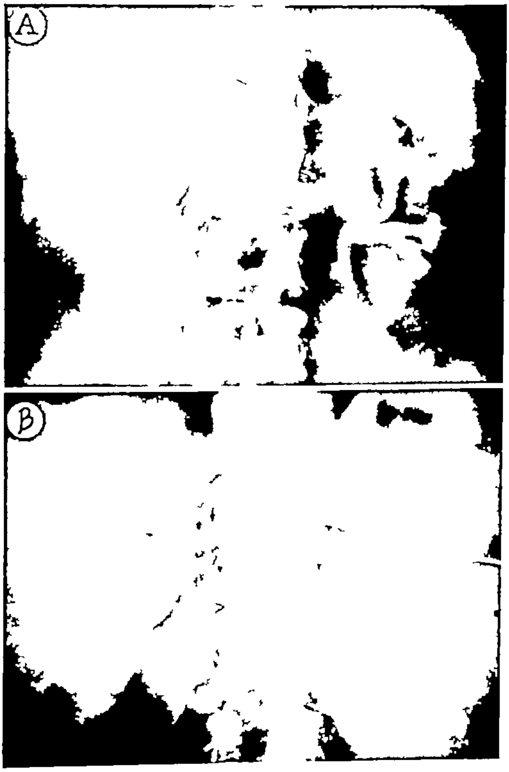

FIG 2 *A*, multiple saccular aneurysms of splenic and renal arteries in 67-year old woman Faint ring shadow overlies infundibulum of upper calyx of left kidney, aortogram, *B*, revealed this shadow to be part of a saccular aneurysm

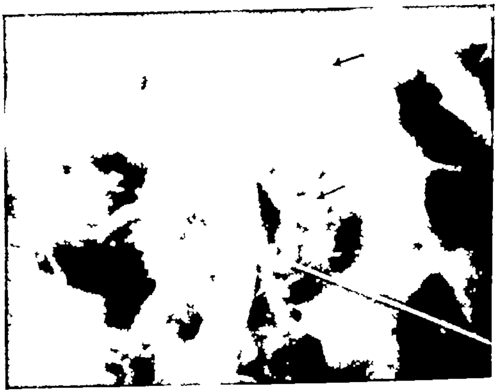

FIG 3 Saccular aneurysms of left renal and splenic arteries (see arrows) in 47 year old woman Note calcific change in the wall of each aneurysm

with partial stenosis of the renal artery had asymptomatic hypertension, but the other 6 patients had normal blood pressure

All three of the patients with arteriosclerotic plaques and poststenotic or jet aneurysmal dilatation of the renal artery had hypertension Two of these patients had the malignant hypertensive syndrome, and aortography in each re-

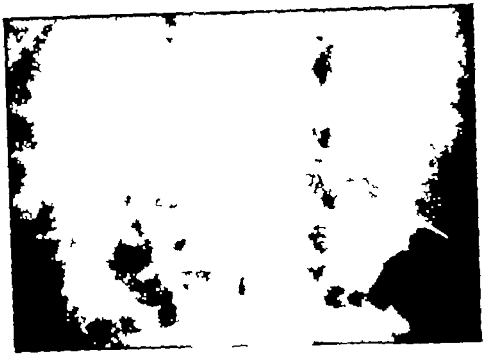

FIG 4 Poststenotic aneurysmal dilatation of left renal artery in 32 year old man with malignant hypertension Point of stenosis (arteriosclerotic plaque) is indicated by arrow Coiled splenic artery is superimposed on renal artery Right kidney circulation is filled, but column of contrast medium in left renal artery has just reached renal hilum This interference with renal blood flow simulates Goldblatt clamp and produces renal hypertension

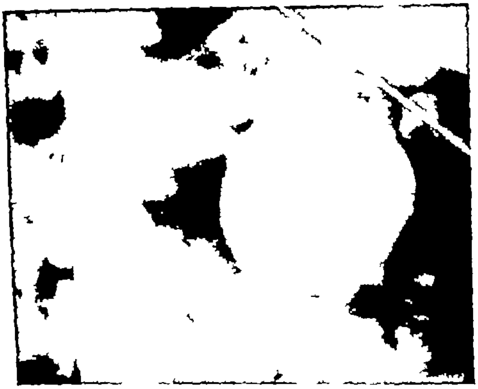

FIG 5 Arteriovenous aneurysm of left renal artery and vein (postnephrectomy) Dilated renal vein is faintly outlined and is superimposed on renal artery

vealed that the arterial lesion was the probable cause of the hypertension That opinion was confirmed in each case when nephrectomy resulted in reversal of the malignant hypertensive syndrome The third patient had benign hypertension and a calcified saccular aneurysm of the right renal artery Aortography revealed a dilatation of the main branch to the upper pole of the opposite kidney, presumably a poststenotic aneurysm (fig 6)

The patient with the noncalcified fusiform aneurysm associated with a large renal tumor had no renal symptoms Routine roentgenography of the chest revealed a solitary pulmonary tumor which was excised and proved to be metastatic renal cell carcinoma Intravenous urography then revealed the source of the tumor

The patient with the arteriovenous aneurysm had no symptoms referable to the lesion The intern heard a loud bruit or murmur over the lower left chest, which was loudest over the old nephrectomy scar The tentative diagnosis of aneurysm was later confirmed by aortography

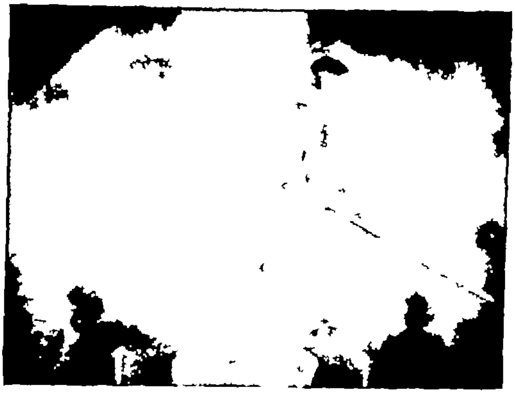

FIG 6 Saccular aneurysm of right renal artery and poststenotic aneurysmal dilatation of upper branch of left renal artery in 42-year old woman who has benign hypertension

Other authors[2 7 10] have stressed that abdominal pain, hematuria, and palpable mass are common symptoms and signs, but patients with these findings usually have a false or ruptured true aneurysm An intrapelvic or intrarenal rupture of an artery or a true aneurysm will produce massive hematuria

DIAGNOSIS

The most consistent roentgen sign of saccular aneurysm of the renal artery is the calcified ringlike shadow which is usually near the hilum of the affected kidney (fig 7) This sign was present in six of our 7 patients having saccular aneurysm In three of the patients, multiple calcified aneurysms were identified in the splenic and renal arteries The large arteriovenous aneurysm, the fusiform aneurysm in the patient with tumor, and the poststenotic or jet aneurysms had no calcification within their walls Aortography is the only means of demonstrating these types of aneurysms

The most accurate means of establishing the diagnosis is by translumbar aortography Aortography was carried out in all 12 patients of this series without complication and with adequate demonstration of the source of the aneurysm In some instances only partial filling of the aneurysm occurred, probably because of the thick wall of arteriosclerosis or the presence of organized blood clot in the aneurysm

It is interesting to note that four other patients had opaque, incomplete ring shadows close to the renal hilum which simulated aneurysms These ranged in diameter from 1 to several centimeters Aortography showed clearly that these lesions were either small calcified arteriosclerotic plaques in the wall of the renal artery or longitudinal plaque formation along a tortuous branch of the renal artery, without encroachment of its lumen (fig 8) It is important to differentiate arteriosclerotic plaque formation in the wall of the renal artery from aneurysm because of the great difference in treatment and prognosis This can only be done by aortography

The roentgen differential diagnoses of calcified aneurysm of the renal artery, as listed by von Ronnen,[1] include 1) calcified aneurysm of the splenic, hepatic,

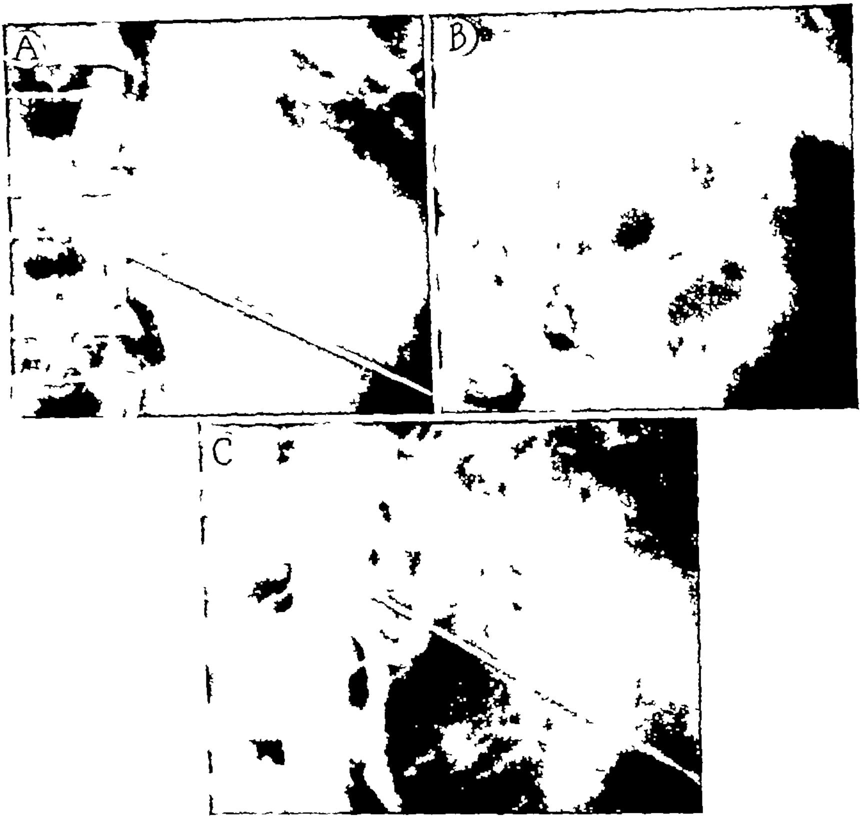

FIG 7 A, saccular aneurysm of upper branch of left renal artery in unusual location, aneurysm resembles renal calculus or calcified tumor *B*, calcification appears to lie adjacent to upper calyx *C*, aortogram demonstrates that it is a saccular aneurysm of a branch of renal artery See figure 10 for method of treatment

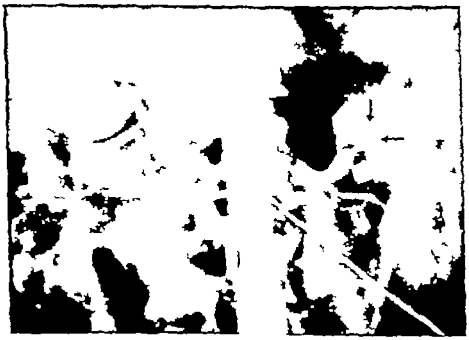

FIG 8 Calcification in wall of renal artery may resemble aneurysm Arrows point to linear calcification

pancreatic, and mesenteric arteries, 2) renal calculus, 3) gallstone, 4) calcified renal cyst, 5) calcified mesenteric lymph nodes, and 6) calcifications in tumors of the kidney and calcified tuberculous foci in the kidney In most instances, however, the roentgen diagnosis of calcified aneurysm of the renal artery presents no difficulties

TREATMENT

Of the 7 patients with saccular aneurysm, four underwent nephrectomy, two had excision of the aneurysm and repair of the artery, and one received no specific treatment Of the 4 patients who underwent nephrectomy, one, the patient who had benign hypertension with multiple microaneurysms and partial stenosis of the renal artery, had relief of hypertension after nephrectomy (average blood pressure 180/110 mm Hg preoperatively, and 120/80 mm Hg four months postoperatively) Two patients each had simultaneous left nephrectomy and splenectomy because of saccular aneurysms of both renal and splenic arteries One of these patients died on the fourth postoperative day of encephalomalacia and pituitary necrosis from probable internal carotid thrombosis occurring 2 days before death, and the other is well 3 years postoperatively The fourth patient who underwent nephrectomy for a large painful aneurysm is well 2 years after operation

In the 2 patients who were treated by excision of the aneurysm and repair of the renal artery, the operative procedure involved careful dissection of the renal artery to demonstrate the origin of the aneurysm In each, the aneurysm was more than 2 5 cm in diameter After application of an arterial clamp to the proximal renal artery, the aneurysm is excised by cutting its neck where there

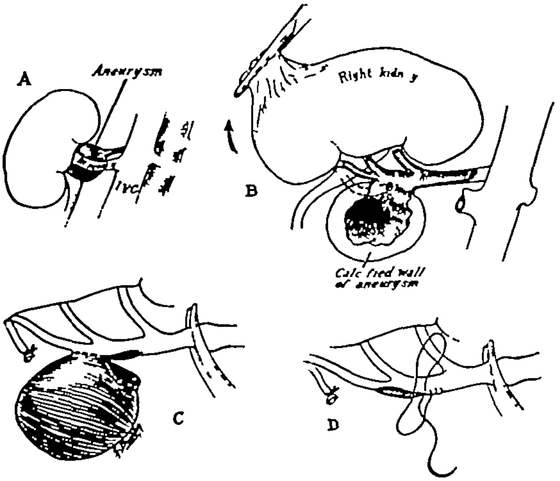

Fig 9 A, anatomic demonstration of aneurysm (see aortogram, fig 6) in relation to renal pelvis and vein *B*, aneurysm and all branches of renal artery are exposed Cutaway drawing demonstrates thick arteriosclerotic wall of aneurysm but its neck is not involved *C*, one distal branch is ligated and aneurysm is excised at its neck *D*, repair of artery (see aortogram, fig 11)

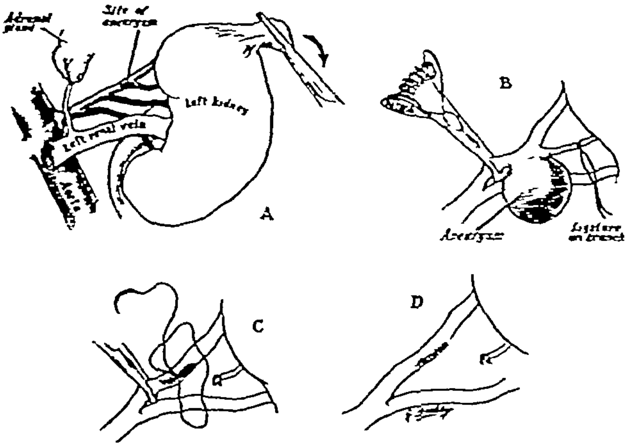

FIG 10 *A*, anatomic demonstration of site of aneurysm shown in fig 7 *B*, small distal branch is ligated and proximal artery clamped before excision of aneurysm *C* and *D*, repair of artery and restoration of circulation

is no palpable evidence of calcified arteriosclerosis (figs 9 and 10) After the removal of the aneurysm, the defect in the renal artery is closed by a simple running arterial suture The clamp is then removed from the renal artery and any points of leakage are quickly repaired by additional sutures In both patients, it was necessary to divide and ligate a small branch on the distal side of the aneurysm which supplied only a small proportion of the renal circulation the other distal main branches remained intact There were no postoperative complications from this procedure In both patients, postoperative urography showed normal renal function, in one, translumbar aortography two weeks after operation demonstrated restoration of normal renal circulation (fig 11, *A*, *B*) Three other authors [15] [16] [17] have reported successful resection of small arteries containing an aneurysm with preservation of the kidney, but there is only one previous report [15] of excision of the aneurysm and repair of the arterial wall

The seventh patient, a 68-year-old woman has multiple calcified congenital aneurysms of both renal arteries and the splenic artery, and has had no specific treatment

Two of the 3 patients with poststenotic or jet aneurysm underwent nephrectomy, both had malignant hypertension and both had remission of the malignant syndrome postoperatively One of these 2 patients, a 65-year-old man, had spontaneous rupture of the abnormal artery five days after the lesion had been

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[14] Mathé, C P Aneurysm of renal artery, report of five cases, one treated by resection of aneurysmal sac without sacrificing kidney J Urol, 60 543-551, 1948

[16] Puigvert Gorro, A and Cols Baques A Aneurisma de la arteria renal Arch españ urol 3 203-210, 1947, cited by Antipa

[17] Orth, O Ein Fall von Traumatischen Aneurysma usw Deutsche Ztschr f chir, 151 272, 1919 cited by Antipa [7]

[15] Callahan, W P and Schultz F H Aneurism of renal artery Surg Gynec & Obst 43 724-728 1926

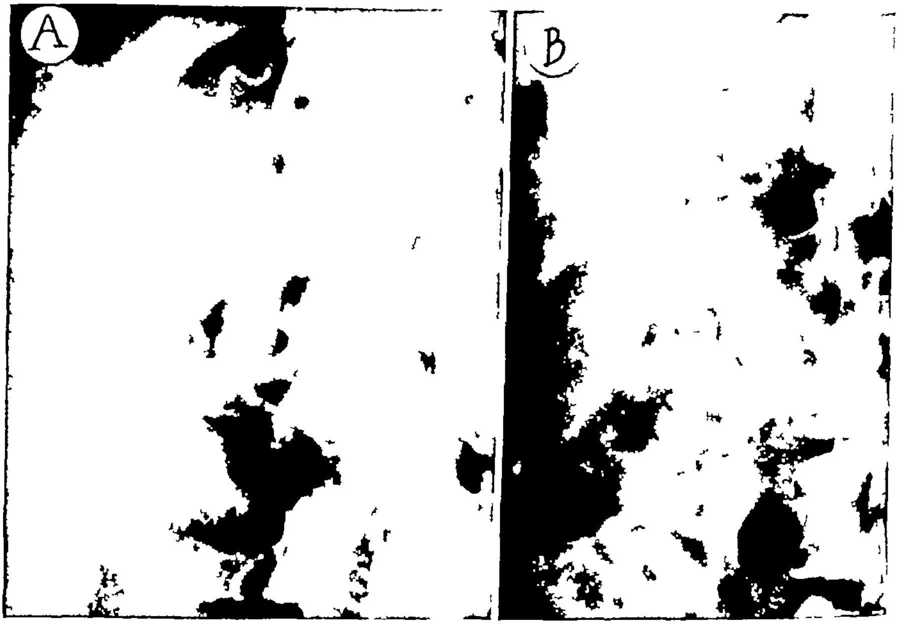

FIG 11 A, right renal artery and B, intravenous urogram 2 weeks after excision of saccular aneurysm (see figs 6 and 9) Round, intensely opaque shadow in lower branch is artifact due to angulation of vessel

demonstrated by translumbar aortography (fig 12) Emergency nephrectomy resulted in remission of the malignant hypertension Three years postoperatively the patient is asymptomatic and has moderately elevated systolic but normal diastolic blood pressure The third patient with poststenotic aneurysm (fig 6) is under medical antipressor therapy for hypertension 6 months after successful excision of the congenital aneurysm of the opposite renal artery Surgical treatment of the remaining aneurysm is under consideration

The patient with the renal tumor and the noncalcified fusiform aneurysm underwent nephrectomy but died 6 months later of metastasis The patient with the large arteriovenous aneurysm had uneventful excision of the lesion transabdominally with division and ligation of the renal artery and vein separately

It is widely known that aneurysms of the renal artery may rupture and cause the patient's death [2] Most if not all instances of rupture, however, have occurred in patients having noncalcified aneurysm of the renal artery, as in the interesting case reported by Pastor and associates [11] In this series of 12 patients, rupture occurred in only one—the elderly hypertensive patient having arteriosclerotic plaque and poststenotic dilatation of the left renal artery It is believed that surgical treatment is unnecessary in nonhypertensive patients having small (1 5 cm in diameter or less), asymptomatic, calcified aneurysms, and is advisable in patients having large aneurysms, especially in those who also have symptoms or hypertension Multiple calcified aneurysms of renal, splenic, or other

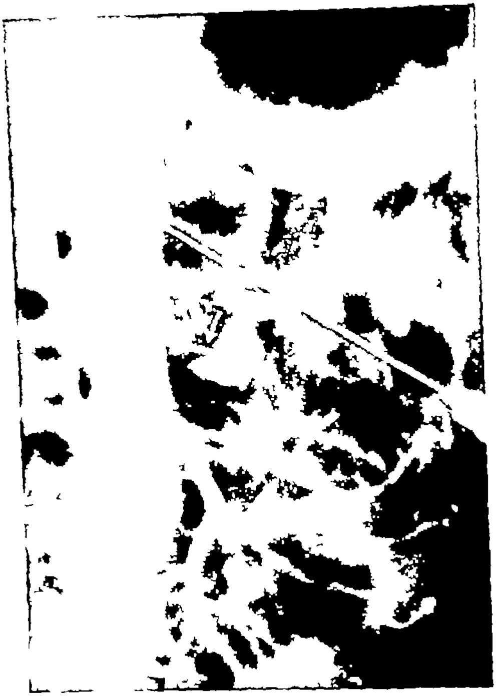

FIG 12 Arrow indicates site of stenosis of left renal artery and poststenotic aneurysmal dilatation in 65 year old man with malignant hypertension Spontaneous rupture occurred 5 days after aortogram had been made Emergency nephrectomy was performed and patient has been well for past 3 years Systolic pressure is moderately elevated, but diastolic pressure is normal

major intra-abdominal arteries are a contraindication to surgery unless symptoms occur Noncalcified aneurysms, particularly those associated with hypertension, should be corrected by nephrectomy or appropriate arterial surgery

CONCLUSION

Renal artery aneurysms probably are more common than autopsy or clinical reports have hitherto indicated Since 1952, 12 patients were observed with various types of renal artery aneurysms Seven of these patients had saccular aneurysms (one had multiple saccular microaneurysms associated with partial stenosis of the renal artery), three had poststenotic or jet aneurysms in association with hypertension, one had a fusiform aneurysm in association with a hypernephroma, and one had a large arteriovenous aneurysm

Aortography is a valuable means of establishing the diagnosis of aneurysm and of differentiating calcified arteriosclerotic plaques within the wall of the renal artery Aortography also has proved of value in the demonstration of unusual noncalcified types of renal artery aneurysm in hypertensive patients

Excision of the aneurysm and repair of the renal artery were performed in two of the patients having congenital saccular aneurysm, postoperatively, normal renal function was demonstrated in each It is believed that large, symptomatic aneurysms, especially in hypertensive patients, should be treated by excision or nephrectomy, whether calcified or not Small, asymptomatic, calcified aneurysms in nonhypertensive patients probably can be followed without surgical treatment

ADDENDUM

Since this manuscript was submitted, the following important report has been published Davidson, R C and Coe, J I Renal artery aneurysm causing malignant hypertension Minn Med , 39 671-674 (Oct) 1956

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EXPERIMENTAL URETERONEOCYSTOSTOMY BY MATHISEN TECHNIQUE

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Anastomosis of the ureter to the bladder under ideal conditions, in the hands of most urologists is successful and without stricture formation However, these same anastomoses may be unsuccessful later due to complications that result from reflux of bladder urine up the reimplanted ureter None of the methods of ureteroneocystostomy now in common use can consistently guarantee a "reflux-proof" anastomosis Searching for a new method of ureterovesical anastomosis, which could consistently prevent reflux, we decided to try the technique Mathisen[1] described in 1953 for ureterocolic implantation His technique, designed to prevent ureteral reflux of colonic contents consisted of forming an intracolonic papilla composed of a full thickness flap of bowel wall wrapped about and sutured to the invaginated ureteral stump with the new ureteral orifice then being at the apex of this papilla He reasoned that such an anastomosis would prevent reflux since the ureteral stoma could not dilate as the bowel became distended and that theoretically too, the same intracolonic pressure would press the nipple or papilla against the bowel wall and close the lumen of the ureter

Nearly two years ago we started to use the Mathisen technique in ureteroneocystostomy in dogs It is of practicular interest to mention now that while our study was in progress Hill Dodson and Hooper[2] reported their results of this same work. Since their methods and their results varied from our own a brief summary of their work is in order They used the Mathisen technique in ureterovesical anastomosis 8 times in 6 dogs, and in each case, the bladder flap included all layers of the bladder wall They then abandoned this procedure because in their dogs, when sacrificed 3 months later the nipples had disappeared They did mention a persistent 2 mm nipple in one case They reported on 2 additional cases using a modified Mathisen technique wherein the bladder flap was composed of only the bladder mucosa with resulting good 6 mm nipples However, they did not recommend this procedure as it was apparently technically difficult Our own results obtained by the standard Mathisen technique have been uniformly successful and later in this paper, comparison of our methods with those of Hill, Dodson and Hooper will I think clarify the differences noted in the end results

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Read at annual meeting, North Central Section of American Urological Association Cleveland Ohio October 3-5 1956

[1] Mathisen Willy A new method for ureterointestinal anastomosis Surg , Gynec & Obst 96 255–258, 1953

[2] Hill J E Dodson, A I Jr and Hooper J W Jr Experimental ureteroneocystostomy using nipple anastomosis technique J Urol 74 596–600 1955

MATERIALS AND METHODS

Eight female dogs were used in this study In each dog, left ureteroneocystostomy was done In seven, the Mathisen technique was used and in 1 dog, a fish mouth type of anastomosis was made for comparison Preoperatively, under intravenous nembutal anesthesia, cystograms were normal and without evidence of ureteral reflux Intravenous pyelograms were also normal

At operation, again under intravenous nembutal anesthesia, a left longitudinal rectus incision was made and the left ureter and the bladder exposed intraperitoneally The left ureter was divided near the bladder and the distal stump ligated with a single 2-0 plain catgut tie A full thickness flap of the bladder (fig 1) was then made on the dome or left lateral wall, wherever it seemed most accessible for the ureter, and with the base of the flap cephalad The ureter was then sutured to this flap with interrupted 5-0 chromic catgut sutures and then the finished nipple tucked intravesically, and the remaining defect in the bladder closed on the outer surface with interrupted 2-0 chromic catgut sutures No drains or indwelling catheters were used

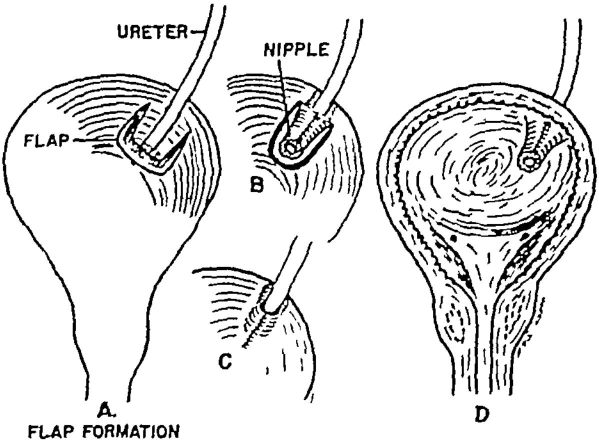

FIG 1 *A*, *B*, *C*, location and formation of Mathisen ureterovesical anastomosis as viewed extravesically *D*, finished intravesical nipple

TABLE I

Case	Type of Anastomosis	Duration (Months)	Location of Transplant	Reflux	Appearance of Kidney Ureter	Nipple & Size	Orifice #4 Fr Cal
I	Mathisen	3	Dome	No	Hydro	Obstructed	No
II	Fish mouth	3	Lateral wall	No	Normal	1 mm	Yes
III	Mathisen	6	Dome	No	Hydro	Obstructed	No
IV	Mathisen	3	Lateral wall	No	Normal	4 mm	Yes
V	Mathisen	6	Dome	No	Normal	6 mm	Yes
VI	Mathisen	7	Lateral wall	No	Normal	5 mm	Yes
VII	Mathisen	7	Dome	No	Normal	7 mm	Yes
VIII	Mathisen	4 5	Lateral wall	No	Normal	15 mm	Yes

RESULTS

Postoperatively all of the dogs did well In the first 2 cases, using the Mathisen technique, complete obstruction at the site of anastomosis occurred with resultant hydronephrosis (table 1) This was probably due to the use of too many

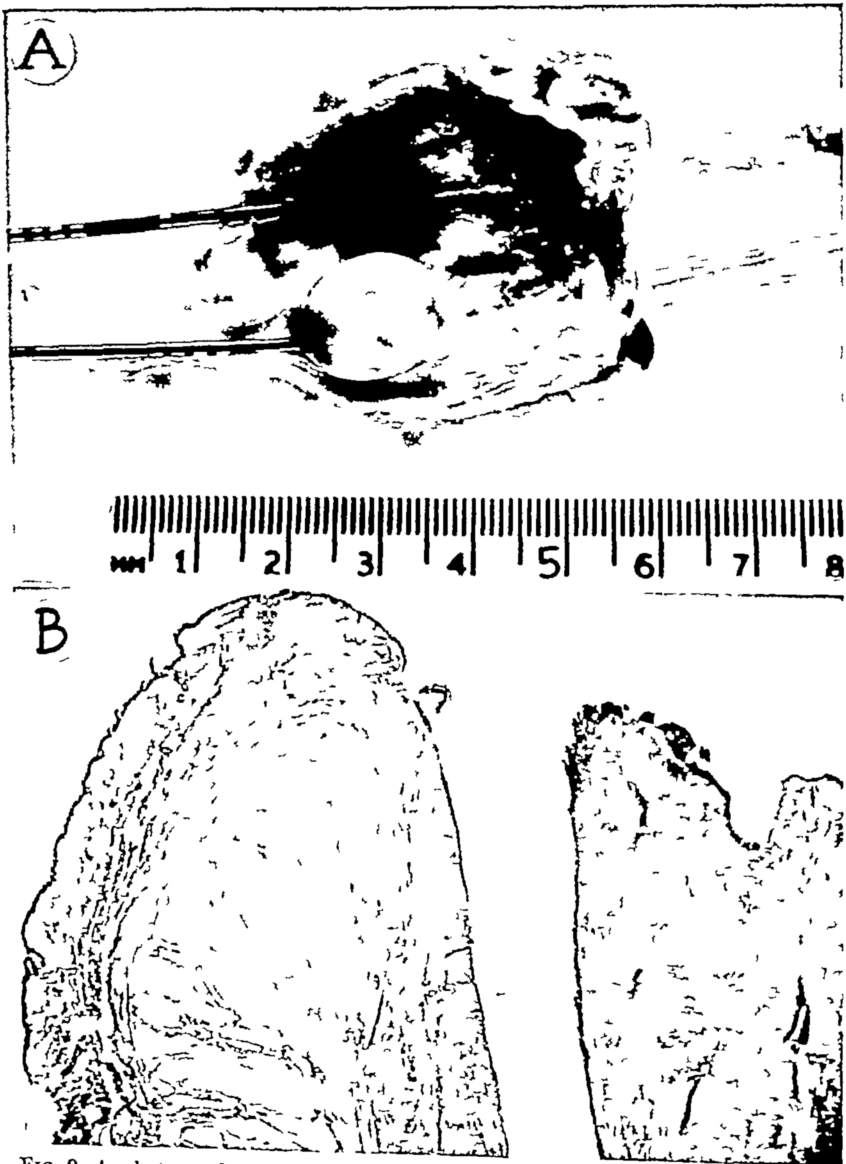

Fig 2 A, photograph of nipple measuring 15 mm after Mathisen type ureteroneocystostomy B, section of nipple showing intact layers including bladder and ureter muscularis noted just left of center

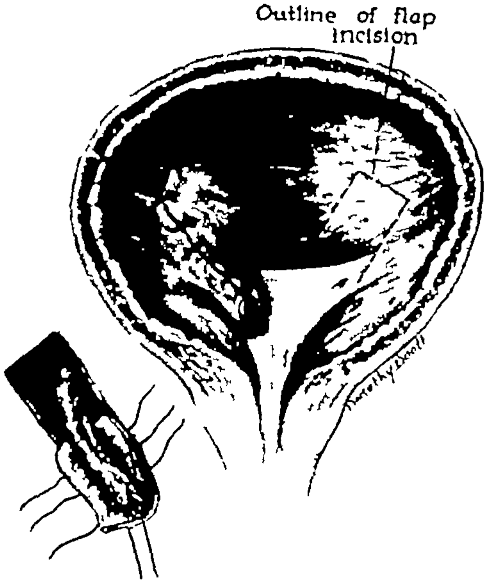

FIG 3 Hill, Dodson and Hooper application of Mathisen technique in ureteroneocystostomy Reprinted by courtesy of authors

sutures, as it did not occur in subsequent cases when the number of sutures used was minimized In the third dog, the fish-mouth technique was used In the remaining 5 dogs, again the Mathisen technique was used and the end results were good In none of these dogs, and indeed in the dog with the fish-mouth technique too, there was no evidence of reflux on cystogram or 20-minute delayed cystograms made 3 months after operation Nor was there any evidence of reflux when the dogs were sacrificed and the bladders were forcibly distended and the cut ends of the lower ureters observed

The dogs were sacrificed from 3 to 7 months postoperatively for an average of 5 5 months All ureteral orifices in the successful cases accommodated a 4F ureteral catheter with ease and the upper urinary tract on the side of operation was normal The papillae, or nipples, formed in the successful cases with the Mathisen technique varied from 4 to 15 mm when measured from the base of the nipple to the tip (fig 2, *A*) The average was 7 4 mm A 1 mm nipple was observed in the dog done with the fish-mouth technique

Microscopic sections of the anastomotic sites were made in the 5 successful Mathisen-type anastomoses As can be seen in figure 2, *B*, the nipples were composed of healthy bladder and ureteral muscularis bearing the same relation as when originally anastomosed

DISCUSSION

We believe that good nipple formation persisted in our successful cases using the Mathisen technique because there was no tension on the ureter at the site of reimplantation Hill et al carried out the same Mathisen technique (fig 3) but their site of anastomosis was just above the trigone with the base of the bladder flap caudad Such an anastomosis, as depicted in their own illustration, of necessity would require increased ureteral length over that which previously normally existed We believe that failure of persistent nipple formation in their cases was due to ureteral tension and retraction Hill[3] has mentioned the possibility that the large bladder muscle bundle attempted to regain its normal contour, and in so doing, caused retraction The fact that they noted 6 mm nipple formation in 2 dogs where the flap consisted of only the bladder mucosa lends credence to this theory

We are well aware of the fact that there was no evidence of ureteral reflux in the dogs without nipple formation, as well as in dogs with good nipple formation However, it would seem that in actual practice resultant nipple formation at the site of anastomosis is desirable and that the added support of functioning bladder muscle about the distal ureter may contribute some sphincter-like action We have not as yet made application of this technique in human beings and cannot forecast the end results

SUMMARY

Application of the Mathisen technique to ureterovesical anastomosis in dogs is presented

The results of the experimental use of the Mathisen technique in ureteroneocystostomy in dogs were generally good, with good nipple formation

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[3] Dodson, A I, Jr Personal communication, 1956

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ILEAL BLADDER SUBSTITUTION AN ANALYSIS OF 78 CASES

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Ileal bladder substitution as a means of urinary diversion was adopted on our service 3½ years ago Personal observation of several patients on whom this procedure had been performed led us to believe that it presented some very definite advantages over ureterosigmoidostomy or ureterointestinal anastomosis into an isolated rectal segment The three principal advantages were an almost complete absence of hyperchloremic acidosis, a markedly reduced incidence of urinary sepsis, and a greater freedom for transplantation of hydronephrotic ureters Subsequent followup evaluation of 78 cases performed during the ensuing period would seem to confirm these advantages

The operation was performed in conjunction with total cystectomy for carcinoma of the urinary bladder in 37 cases, in most instances as a one-stage procedure Palliative diversion without cystectomy was accomplished in 15 cases The procedure was utilized for revision of post-cystectomy ureterosigmoidostomy because of progressive loss of renal function in 4 cases The operation was performed for bilateral ureteral scarring following radiation therapy for carcinoma of the cervix in 7 cases and for non-malignant disease in eighteen The types of non-malignant disease are listed in table 1

It is interesting to note that in the non-malignant disease category four of the patients had prior ureterosigmoidostomy for exstrophy and one had a Boyce-Vest procedure In 7 cases urinary diversion to an ileal segment was accomplished where a permanent neurogenic disease of the bladder existed, and in four of these patients there was already advanced hydronephrosis In the other three, the isolated ileal segment was anastomosed directly to the bladder without reimplanatation of the ureters There was no operative mortality in the non-malignant disease category, and with one exception, all are surviving This patient had extremely advanced renal disease prior to the original surgery

An evaluation of early and late complications is of value in determining the practicality of a procedure of this type Obviously, a considerable amount of surgical technique is involved in establishing the isolated ileal segment and accomplishing the ureteroileal anastomoses Complete familiarity with the technical aspects of the procedure is essential Even with meticulous attention to detail, a certain number of complications are inevitable Our early complications are listed in table 2 In 48 cases, well over 50 per cent of the total, no immediate postoperative complications of significance occurred and the convalescence was completely without major incident Wound dehiscence occurred in a surprisingly high percentage of the cases This complication seemed to occur in spite of unusually careful attention to wound closure including the use of wire sutures Electrolyte disturbance and uremia were present in 3 cases These

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Read at annual meeting of North Central Section of American Urological Association, Cleveland, Ohio, October 3–5 1956

TABLE 1 *Types of non malignant disease*

Revision of ureterosigmoidostomy for exstrophy	4
Revision of Boyce-Vest procedure for exstrophy	1
Exstrophy of the bladder	1
Neurogenic bladder (ileal segment to bladder)	3
Neurogenic bladder with advanced hydronephrosis, bilateral	4
Chronic cystitis, contracted bladder with advanced hydronephrosis	1
Hunner ulcer	1
Extensive crushing injury to pelvis	1
Stricture of urethra with multiple perineal fistulas	2
Irreparable ureterovaginal fistula with solitary kidney	1

TABLE 2 *Complications, early*

None	48
Wound dehiscence	6
Electrolyte disturbance	3
Uremia	3
Pyelonephritis	4
Postoperative ileus	3
Intestinal obstruction	2
Urine leak	2
Tight stoma	2
Skin sensitivity	2
Fecal fistula	1
Miscellaneous	9

individuals had advanced renal disease prior to construction of the ileal segment No electrolyte difficulties were encountered in those patients with normal upper urinary tracts prior to surgery It is noteworthy that the immediate postoperative incidence of pyelonephritis is quite low All patients received prophylactic chemo- or antibiotic therapy during the early period of convalescence Urine leakage occurred in 2 patients but ceased spontaneously in one, the other requiring incision and drainage

Although present in only 2 cases, a tight ileal stoma requires special emphasis Every effort should be made during the construction of the ileal segment to assure an adequate opening in the skin, fascia, and peritoneum of the abdominal wall through which the ileal segment is brought It is now our custom to check patency of the ileal segment within the first three or four days and to follow through with regular digital dilatations for a fairly prolonged period at increasing intervals postoperatively We recently had occasion to observe a patient who experienced severe pain in the left upper abdomen on the fifth postoperative day The exact cause of the pain was not readily apparent However, on further investigation the ileal stoma was found to be quite tight and the ileal segment contained 125 cc residual urine The temporary insertion of a large urethral catheter into the ileal segment corrected the situation immediately and repeated dilatation of the stoma insured a good permanent result

Skin sensitivity has created a genuine problem in only 1 case For the most

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It is interesting to note that in the non-malignant disease category four of the patients had prior ureterosigmoidostomy for exstrophy and one had a Boyce-Vest procedure In 7 cases urinary diversion to an ileal segment was accomplished where a permanent neurogenic disease of the bladder existed, and in four of these patients there was already advanced hydronephrosis In the other three, the isolated ileal segment was anastomosed directly to the bladder without reimplanatation of the ureters There was no operative mortality in the non-malignant disease category, and with one exception, all are surviving This patient had extremely advanced renal disease prior to the original surgery

An evaluation of early and late complications is of value in determining the practicality of a procedure of this type Obviously, a considerable amount of surgical technique is involved in establishing the isolated ileal segment and accomplishing the ureteroileal anastomoses Complete familiarity with the technical aspects of the procedure is essential Even with meticulous attention to detail, a certain number of complications are inevitable Our early complications are listed in table 2 In 48 cases, well over 50 per cent of the total, no immediate postoperative complications of significance occurred and the convalescence was completely without major incident Wound dehiscence occurred in a surprisingly high percentage of the cases This complication seemed to occur in spite of unusually careful attention to wound closure including the use of wire sutures Electrolyte disturbance and uremia were present in 3 cases These

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Read at annual meeting of North Central Section of American Urological Association, Cleveland, Ohio, October 3–5 1956

TABLE 1 *Types of non-malignant disease*

Revision of ureterosigmoidostomy for exstrophy	4
Revision of Boyce Vest procedure for exstrophy	1
Exstrophy of the bladder	1
Neurogenic bladder (ileal segment to bladder)	3
Neurogenic bladder with advanced hydronephrosis, bilateral	4
Chronic cystitis, contracted bladder with advanced hydronephrosis	1
Hunner ulcer	1
Extensive crushing injury to pelvis	1
Stricture of urethra with multiple perineal fistulas	2
Irreparable ureterovaginal fistula with solitary kidney	1

TABLE 2 *Complications, early*

None	48
Wound dehiscence	6
Electrolyte disturbance	3
Uremia	3
Pyelonephritis	4
Postoperative ileus	3
Intestinal obstruction	2
Urine leak	2
Tight stoma	2
Skin sensitivity	2
Fecal fistula	1
Miscellaneous	9

individuals had advanced renal disease prior to construction of the ileal segment. No electrolyte difficulties were encountered in those patients with normal upper urinary tracts prior to surgery. It is noteworthy that the immediate postoperative incidence of pyelonephritis is quite low. All patients received prophylactic chemo- or antibiotic therapy during the early period of convalescence. Urine leakage occurred in 2 patients but ceased spontaneously in one, the other requiring incision and drainage.

Although present in only 2 cases, a tight ileal stoma requires special emphasis. Every effort should be made during the construction of the ileal segment to assure an adequate opening in the skin, fascia, and peritoneum of the abdominal wall through which the ileal segment is brought. It is now our custom to check patency of the ileal segment within the first three or four days and to follow through with regular digital dilatations for a fairly prolonged period at increasing intervals postoperatively. We recently had occasion to observe a patient who experienced severe pain in the left upper abdomen on the fifth postoperative day. The exact cause of the pain was not readily apparent. However, on further investigation the ileal stoma was found to be quite tight and the ileal segment contained 125 cc residual urine. The temporary insertion of a large urethral catheter into the ileal segment corrected the situation immediately and repeated dilatation of the stoma insured a good permanent result.

Skin sensitivity has created a genuine problem in only 1 case. For the most

TABLE 3

Metastatic or recurrent carcinoma	8
Tight stoma	6
Pyelonephritis	6
Progressive hydronephrosis (unilateral)	4
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Verrucae around stoma	2
Incisional hernia	2
Calculus	2
Acidosis	2
Intestinal obstruction	1
Progressive eversion of stoma	1

TABLE 4 *Renal status*

Unchanged	33
Normal preoperatively	17
Improved	26
Reduced	7
Normal preoperatively	4

part local irritation of the skin about the stoma has resulted either from poor hygienic management of the bag and the cement used to fasten it to the abdominal wall, or was due to the presence of too large an opening in the ileal bag The opening in the bag should be almost exactly the same size as the circumference of the ileal stoma

Late complications are listed in table 3

As would be anticipated in dealing with advanced carcinoma, the major complication was metastatic or recurrent carcinoma Tight stoma occurred in 6 cases and has presented the principal technical complication which we have encountered In some instances minor surgical revision has been necessary As mentioned previously, careful attention to the formation of the stoma and repeated digital dilatations can obviate this complication in most cases An adequate stoma with free drainage is absolutely essential to the overall success of the procedure When stenosis occurs there is secondary stagnation of urine with resultant progressive hydronephrosis and recurrent infection

Clinical pyelonephritis occurred in 7 7 per cent of the cases, a very acceptable figure in comparison with the 40 to 50 per cent incidence usually encountered following ureterosigmoidostomy In no patient was the urine from the ileal segment sterile on culture and all cases contained a significant number of white blood cells However, we did not consider pyelonephritis as existing unless there was clinical evidence of urinary sepsis such as chills, fever, or costovertebral angle tenderness

Progressive hydronephrosis occurred in 4 cases, requiring surgical revision In all cases intravenous pyelography was performed at 3 month intervals during the first year to discover the possible development of non-symptomatic pro-

gressive hydronephrosis The presence of uremia and acidosis occurred only in those patients who had severely damaged kidneys prior to surgery Although a fairly high incidence of intestinal obstruction was anticipated, it occurred in a surprisingly small number of cases

Surprisingly few patients have complained of mechanical difficulty in management of the ileostomy bag Verrucae appeared about the stoma in 2 cases This complication was due to poor fitting of the bag there being too large an area of skin exposed to urine A reduction in the size of the bag opening immediately corrected the problem

The overall renal status as judged by intravenous urography, elevation of nonprotein nitrogen, the presence of acidosis, or recurrent urinary sepsis, was rated as listed in table 4 In thirty three cases, the renal status remained unchanged Seventeen of these were considered normal prior to operation In twenty six cases there was a definite improvement in the overall renal picture In only seven cases was there a definite deterioration of renal function following surgery In four of these normal preoperative pyelograms were present From an overall renal standpoint one could consider the results as satisfactory in approximately 91 1 per cent of the cases These results compare quite favorably with late results following other types of urinary diversion

SUMMARY

A series of 78 cases of ileal bladder substitution performed over the past 3½ years has been reviewed The various early and late complications have been discussed

In our opinion, implantation of ureters into an isolated ileal segment has proved to be a satisfactory method of urinary diversion

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The patient had the appearance of an acutely ill moderately dehydrated woman whose temperature was 98F and the blood pressure reading 130 80 Abdominal distention, generalized abdominal tenderness and rebound phenomenon were noted in the left lower quadrant Borborygmi were infrequent No costovertebral angle tenderness was noted. On pelvic examination the cervix was firm and tender on manipulation Rectal examination disclosed anterior vault tenderness Feces on the examining finger was normal

Urinalysis was noted to be grossly bloody No other elements were noted in the sediment A complete blood count showed hemoglobin 12.1 gm. white blood cells 8,950 with a moderate shift to the left Abdominal decubitus films were thought to be compatible with a paralytic ileus and abdominal fluid No free air was seen The film was interpreted as suggestive of intermittent bowel obstruction

Cystoscopic examination revealed several small blood clots on the floor of the bladder High on the posterior surface of the bladder a small ulcerative lesion with "puckering" was seen A catheter could be introduced into the center of the lesion for a short distance No injection of this tract was made The bladder otherwise appeared normal except for mild erythema A tentative working diagnosis of diverticulitis of the left colon with impending perforation into the bladder was made Barium enema failed to confirm this diagnosis

Antibiotic therapy with oxytetracycline was instituted and the patient was given general supportive therapy with an anchored urethral catheter to evaluate urine output which was satisfactory Gradual clinical improvement was noted She however did continue to have gross hematuria A cystogram made November 25 1955 disclosed evidence of intraperitoneal extravasation of contrast medium from the bladder (fig 1 A) Surgical exploration was then accomplished under general anesthesia through a midline suprapubic incision The peritoneal cavity was entered and the sigmoid colon found to be attached to the bladder The sigmoid colon was gently manipulated to mobilize it from the bladder. In so doing suddenly the entire upper two-thirds of the bladder purple gangrenous

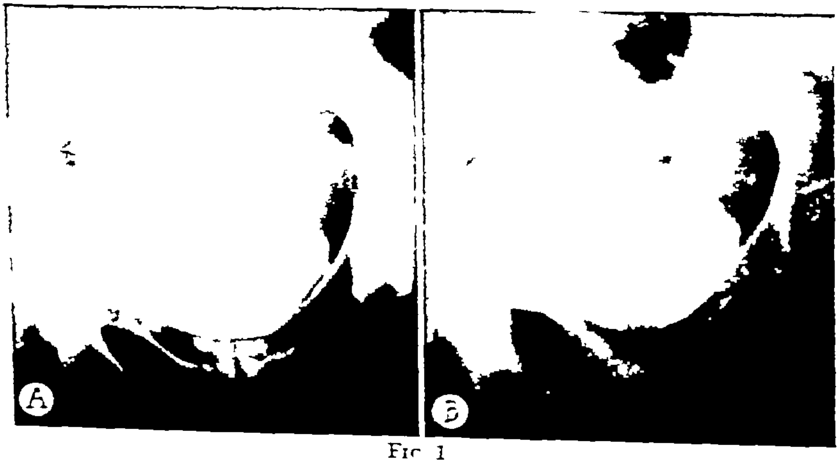

Fig 1

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REGENERATION OF BLADDER CASE REPORT

ROBERT A GARRETT AND WALTER R VAUGHN*

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The practical surgical possibilities embodied in bladder (as well as ureter) regeneration has captured the interest of a large segment of urologic surgeons This is not a new concept Folsom,[1] in 1940, was impressed with apparently normal bladder capacity following extensive subtotal resection of the urinary bladder for Hunner ulcer A total of 8 cases were reported with subsequent ureteral reflux and infection Subtotal cystectomy in dogs was done leaving the vesico-urethral orifice and trigone Restoration of bladder capacity and bladder weight followed Microscopic study of sections of bladders thus regenerated disclosed normal muscle layers It was Folsom's conclusion that, "since no definite evidence of hypertrophy is observed and since hypertrophy alone would not account for a replacement in kind of all the layers of the bladder wall the reestablishment of functioning bladder must be considered as evidence of regeneration in the dog " Renascence of interest in this subject was stimulated by Bohne[2] in 1955 after careful and ingenious work with dogs using plastic molds about which new bladders were found to form Such new pouches were found to be lined with transitional epithelium and contained smooth muscle in their walls Observations in human patients whose bladder either was surgically excised or underwent total or subtotal destruction and in whom subsequent bladder regeneration occurred are few Richardson[3] has recorded observations in a patient, remarkably similar to that herein reported, whose bladder underwent necrosis followed by regeneration Opportunity to closely observe such a patient prompts this report It has been possible to examine our patient cystoscopically, cystometrically and by biopsy of the new bladder

CASE REPORT

A 41-year-old-colored female hospital attendant was admitted to the Indiana University Medical Center November 16, 1953, six weeks after bilateral inguinal herniorrhaphy She had had an uneventful convalescence from surgery until 4 days prior to admission at which time aching pain developed in the left lower quadrant of the abdomen near the site of herniorrhaphy After spontaneous disappearance of this pain 2 days prior to admission, she experienced a recurrence of the same type of discomfort Vomiting, diarrhea and finally loss of consciousness occurred in the 24 hours prior to admission Abdominal pain became generalized and accompanied by chills Total gross painless hematuria was experienced on the evening prior to admission

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Read at annual meeting, North Central Section of American Urological Association, Cleveland, Ohio, October 3–5, 1956

* *Present address*—615 Dubois Street, Vincennes, Indiana

[1] Folsom, A I , O'Brien, H A and Caldwell, G T Subtotal cystectomy for Hunner ulcer J Urol , 44 650–666, 1940

[2] Bohne, A W , Osborn, R W and Hettle, P J Regeneration of the urinary bladder in the dog, following total cystectomy Surg Gynec & Obst , 100 259–264, 1955

[3] Richardson, E J Bladder regeneration Minn Med , 35 547–549, 1952

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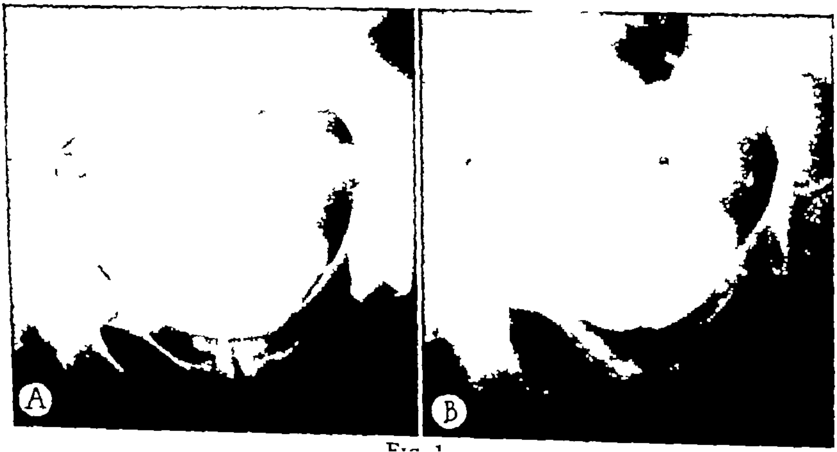

Fig 1

and edematous, came away from the bladder fossa attached to the sigmoid The remainder of the bladder could be seen in its fossa, necrotic as its separated component The Foley catheter was discerned lying in the necrotic mass of tissue Both aerobic and anaerobic cultures of the necrotic tissue were obtained at this time without subsequent growth No frank suppuration was seen at any time Ureteral orifices could not be identified in the necrotic mass It is entirely conceivable that the trigone still was viable although it could not be so visualized During the procedure a copious amount of urine welled up from the floor of the necrotic bladder

The proposition of urinary diversion immediately presented itself Ureterosigmoidostomy or ileal loop diversion was deemed inadvisable because of insufficient bowel preparation and magnitude of the procedures Ureterocutaneous transplantation was felt unwise because of the finality of this rather unsatisfactory urinary diversion technique It was noted at this point that the uterus was of large size together with rather large fallopian tubes representing bilateral hydrosalpinx By plicating each fallopian tube, attaching it laterally to the lateral pelvic wall, broad ligament and anteriorly to the anterior abdominal wall, together with anterior fixation of the fundus of the uterus, it was possible to fashion a urinary compartment in the anterior pelvis (fig 2) It was not in our most optimistic thoughts that this compartment might be watertight A 24F foley catheter was placed into the urinary receptacle thus formed and the anterior abdominal wall closed about the catheter The peritoneum was closed superiorly without drainage The segment of the colon attached to the necrotic bladder was exteriorized in Bloch (Heinecke-Mikulicz) fashion through a separate

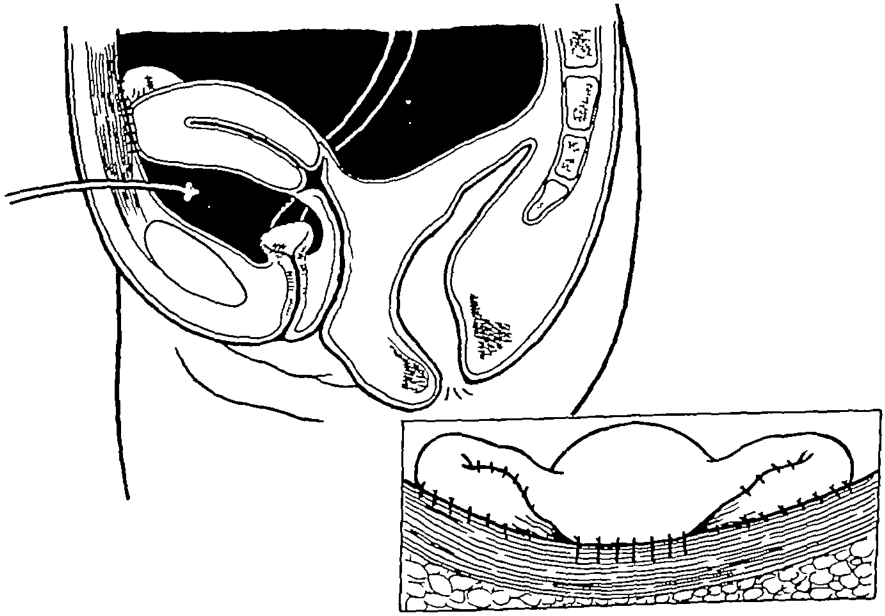

Fig 2

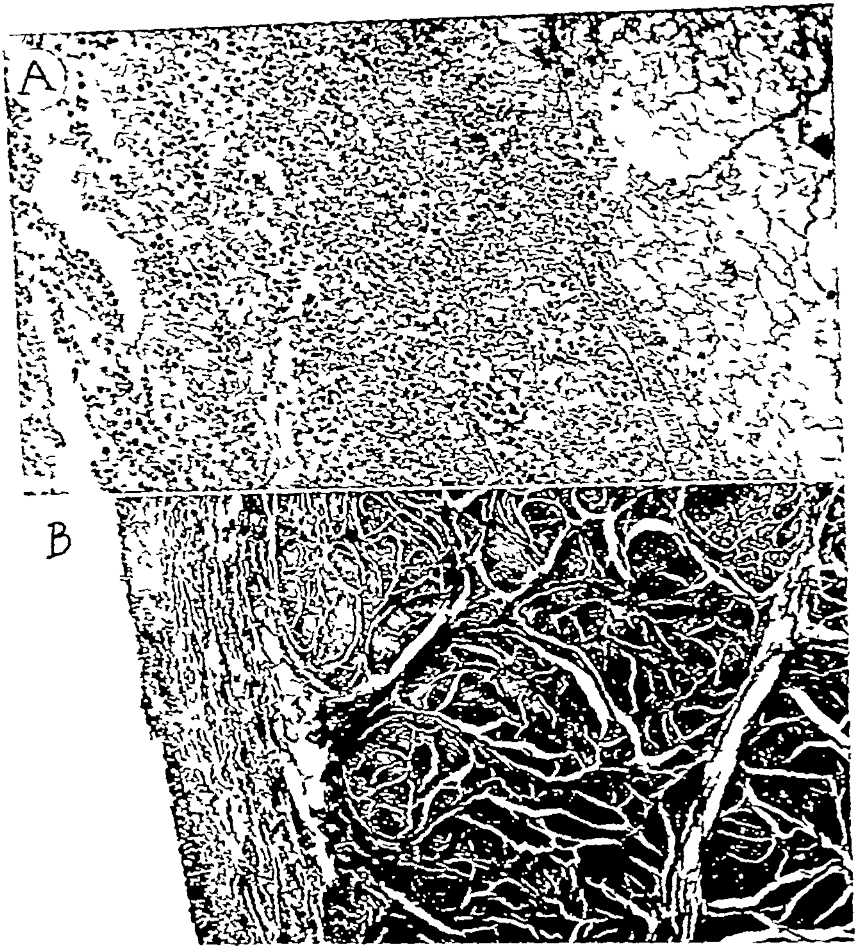

Fig 3

abdominal incision Subsequently the exteriorized bowel was excised and the colostomy thus formed reanastomosed intraperitoneally at a subsequent surgical procedure The patient's postoperative course was surprisingly good Appropriate antibiotic therapy was instituted Continuous suction applied to the suprapubic catheter promoted more or less complete emptying of the pelvic pouch On the fourth postoperative day the suprapubic tube failed to irrigate properly—the solution returned around the tube The urethral catheter which had been allowed to remain in place irrigated easily By the tenth postoperative day the patient was up without complaints and urine was grossly clear On the fourteenth postoperative day she was transported to the cystoscopic room where a cystogram was obtained and interpreted as having the configuration of a normal bladder (fig 1, *B*) Urinalysis at this time was negative save for an occasional red blood cell

Pathologic report on tissue removed at the time of surgery was gangrenous cystitis Microscopic section revealed complete necrosis of mucosa, submucosa and muscularis of the bladder In the subserosal fat there was extensive infiltration of lymphocytes, histiocytes as well as a marked proliferation of capillaries and fibroblastic elements In some areas this reaction extended to the serosa No evidence of malignancy was found (fig 3, *A*)

On the twenty-fourth postoperative day cystoscopy was done The bladder mucosa, appearing *perfectly normal, was seen to be thrown in folds and with* proper distention these folds ironed out as is normally seen Both ureteral orifices were identified and appeared normal The trigone appeared normal and the bladder capacity was 450 cc Following cystoscopy the urethral catheter was removed and the patient was unable to void The suprapubic catheter was removed and the urethral catheter reanchored Three days after cystoscopy a cystometrographic study was done and is recorded in figure 4, as is a subsequent cystometrogram September 14, 1956

On January 2, 1955 the urethral catheter was removed after which the patient voided, the residual urine was 100 cc Micturition was accomplished easily and the patient was asymptomatic After discharge on January 6 she returned to the outpatient department where re-examination revealed no residual urine Subsequent visits to the outpatient clinic disclosed a midline ventral hernia, *the patient having complaints referable to this weakness* Only occasional

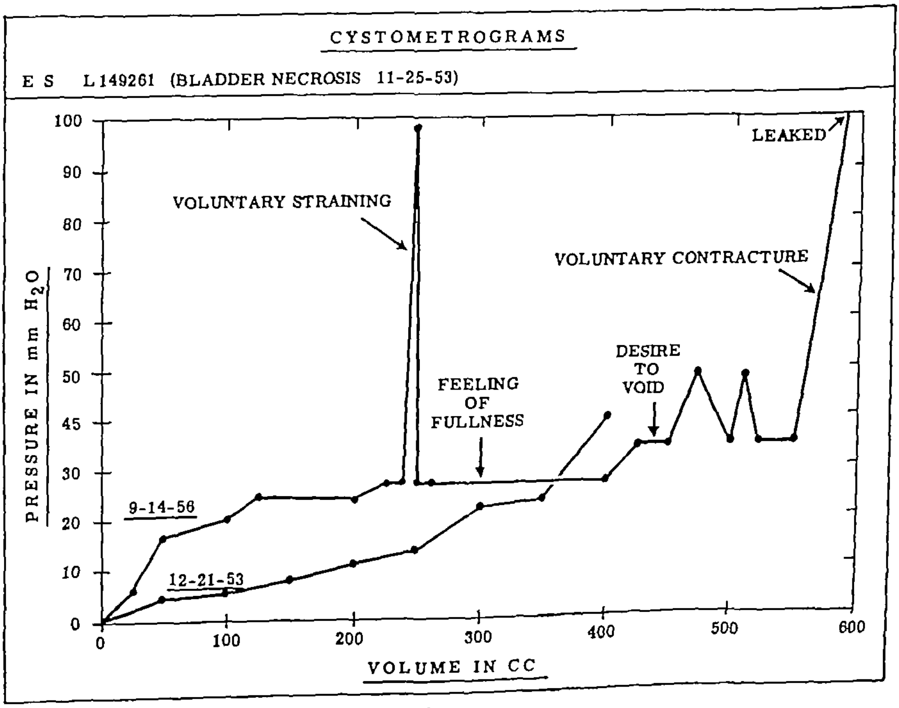

FIG 4

episodes of frequency, urgency, and nocturia of a mild degree were related Urinalyses repeatedly were normal

Readmission was effected February 12, 1955 for repair of the ventral hernia Physical findings were limited to the midline hernia area An intravenous pyelogram was obtained and thought to be within normal limits On February 16 the patient was returned to surgery where the incisional hernia was repaired with some difficulty The bladder was palpated on exposing the midline area and felt to be normal A biopsy taken from the anterosuperior aspect of the bladder disclosed chronic cystitis Postoperative course was uneventful and the hernia was satisfactorily repaired On section the urinary bladder was lined with transitional epithelium Moderate numbers of lymphocytes were scattered throughout the tunica propria Muscularis propria was essentially normal (fig 2, *B*) The patient was discharged March 3 and has been seen repeatedly in the outpatient clinic with no complaints referable to bladder or repaired hernia sites

DISCUSSION

Three salient points of discussion are evident 1) What pathologic entity gave rise to bladder gangrene? 2) How complete was the bladder gangrene? 3) Did bladder regeneration actually occur?

We are forced to answer the first question by a somewhat nebulous diagnosis of idiopathic gangrene of the bladder The cause for this unusual disturbance was not evident from bacteriologic culture studies Both aerobic and anaerobic media failed to manifest growth Examination of the colon at its point of adherence to the bladder did not show acute diverticulitis as was suspected The appearance of the bowel at that point was edematous, inflamed but no definite diagnosis other than colitis could be attached to it

In answer to the second question, how extensive was bladder necrosis, it can be safely said that all but the trigone of the bladder was necrotic and perhaps this structure was too Exposure in the bladder fossa was difficult to obtain and numerous pieces of sloughed tissue that obscured the trigone made definite assessment of this feature impossible Biopsy in the trigonal area did not seem feasible In the process of surgical exploration practically all of the necrotic tissue was debrided away and could not have formed a framework upon which new bladder could reform Fully two-thirds of the bladder was exteriorized with the adherent bowel

In answer to the third question, did the bladder regenerate, we believe that we can answer in the definite affirmative Cystoscopic and cystometric study indicated that a normal appearing receptacle exerted nearly normal muscular tone Cystometric studies were taken early in the course of convalescence and have since returned to a normal pattern Certainly biopsy tissue obtained from the bladder structure should confirm the concept that regeneration has taken place In that regard it is quite likely that sufficient trigone and overlying transitional epithelium survived necrosis to allow a nucleus of tissue elements from which a new bladder could form

SUMMARY

A case report of idiopathic necrosis of the bladder has been presented Cystographic, cystoscopic and cystometrographic studies have indicated that regeneration of the bladder muscle and mucosa has occurred A biopsy of the bladder at subsequent surgical intervention seems to confirm the regeneration of this hollow viscus

The authors wish to acknowledge with gratitude pathologic consultation by Dr Frank Vellios, and medical illustrative assistance by Mr James Glore

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EXPERIENCE WITH URINARY BLADDER REGENERATION

A. WAITE BOHNE AND K. L. URWILLER

From Department of Urology, Henry Ford Hospital, Detroit, Mich.

The many pitfalls associated with diversion of the upper urinary tract are well known to all urologists. In an attempt to overcome some of these difficulties, experimental work on bladder regeneration was started in 1950. The animal used was the dog and the results of these experiments have been recorded.[1]

Subsequently, seven human cases have been performed, and it is desired now to present these. Reasons for the operative procedure were as follows: 2 cases of severe, chronic, intractable interstitial cystitis, 4 cases of diffuse carcinoma of the bladder, and 1 case of arrested urinary tract tuberculosis.

Because of changes in technique and equipment since the previous publication it might be well to describe briefly the procedure used.

PROCEDURE

Cystectomy is performed through a suprapubic transverse incision. After mobilization of the bladder and in some cases the prostate, the urethra is transected at the urethrovesical or the urethroprostatic junction. The ureters are severed as near to the ureterovesical junction as possible. This will vary, of course, with the patient's illness. In case of subtotal cystectomy, the trigone of the bladder is left intact including the ureteral orifices. After the whole or greater part of the bladder has been removed, the plastic mold is then ready to be placed in the pelvis (fig. 1, *A* and *B*). A distensible rubber bag secured to a catheter has been previously inserted into the plastic mold. No. 8F ureteral catheters are passed in a retrograde manner to the renal pelves. The severed ends of the ureters are allowed to ride freely over these catheters. The urethral portion of the mold is inserted in an antegrade manner through the urethra in the female or through a perineal urethrostomy in the male. When the catheters have been adjusted and the mold in position, the distensible bag is then inflated with air to the capacity of the mold (fig. 1, *C*).

From the observations on animals, the molds have been left in place 90 days after which the bag is deflated and the mold, bag, and catheters are removed merely by pulling them through the urethra.

CASE REPORTS

A. G. was a 54-year-old woman with multiple carcinomas of the bladder. A subtotal cystectomy was performed August 1, 1953 and a plastic mold inserted. In this first case, a rigid, hollow mold was used. Because of poor drainage from the ureteral catheters, the mold was removed suprapubically 6 weeks later with readjustment of the ureteral catheters. The postoperative course was then pro-

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Read at annual meeting, North Central Section of American Urological Association, Cleveland, Ohio, October 3-5, 1956.

[1] Bohne, A. W., Osborne, R. W. and Hettle, P. J.: Regeneration of the urinary bladder in the dog following total cystectomy. Surg., Gynec. & Obst., 100: 259-264, 1955.

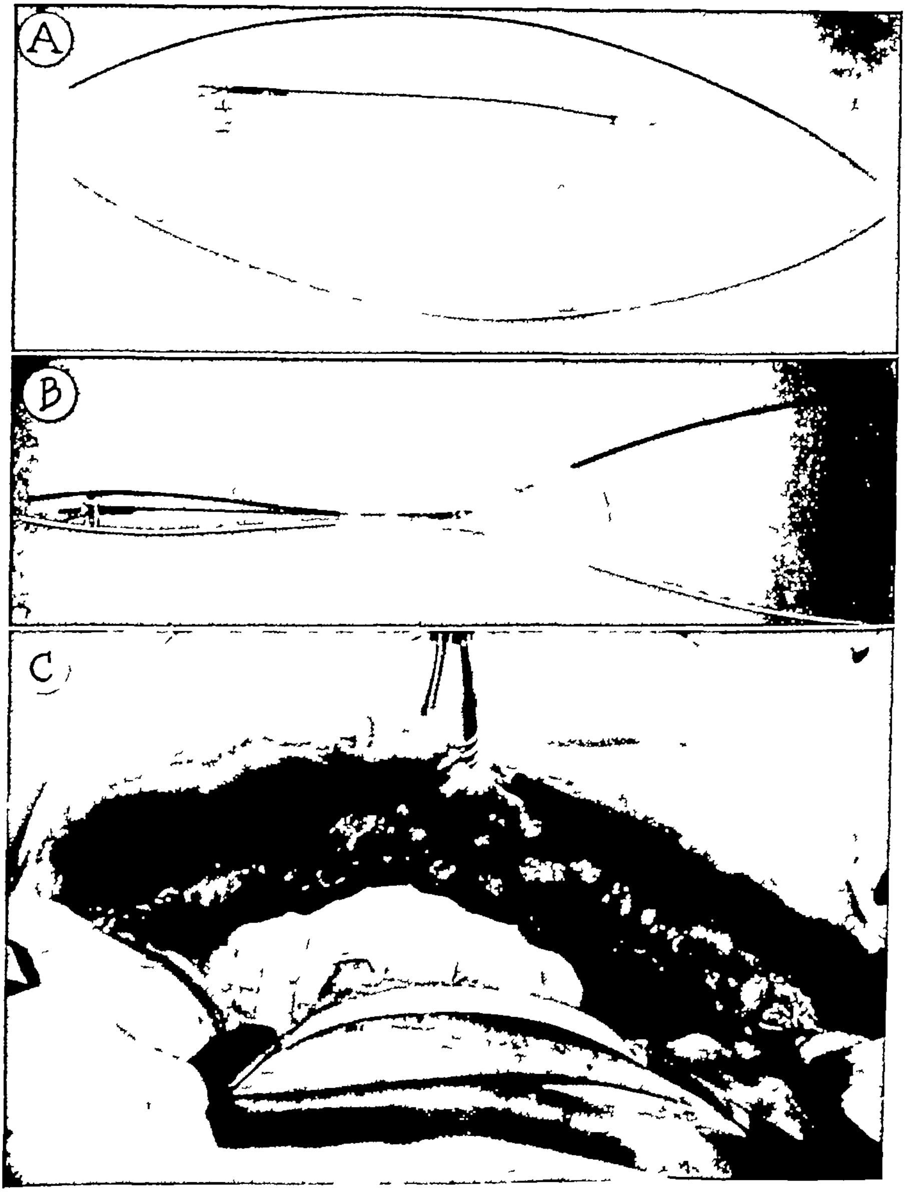

FIG 1 *A* and *B*, plastic mold, distensible bag and catheters *C*, plastic mold in place

gressing quite well until thrombophlebitis developed, and the patient expired 12 days after the second procedure from a pulmonary embolus

At autopsy, the regenerated urinary bladder was of fair size (fig 2, *A*) No epithelial lining was seen due to autolysis caused by a time delay in obtaining the post mortem (fig 2, *B*) The inner layers of the bladder were composed of granulation tissue which was exceedingly vascular and showed marked infiltration with lymphocytes, macrophages and occasional polymorphonuclear cells

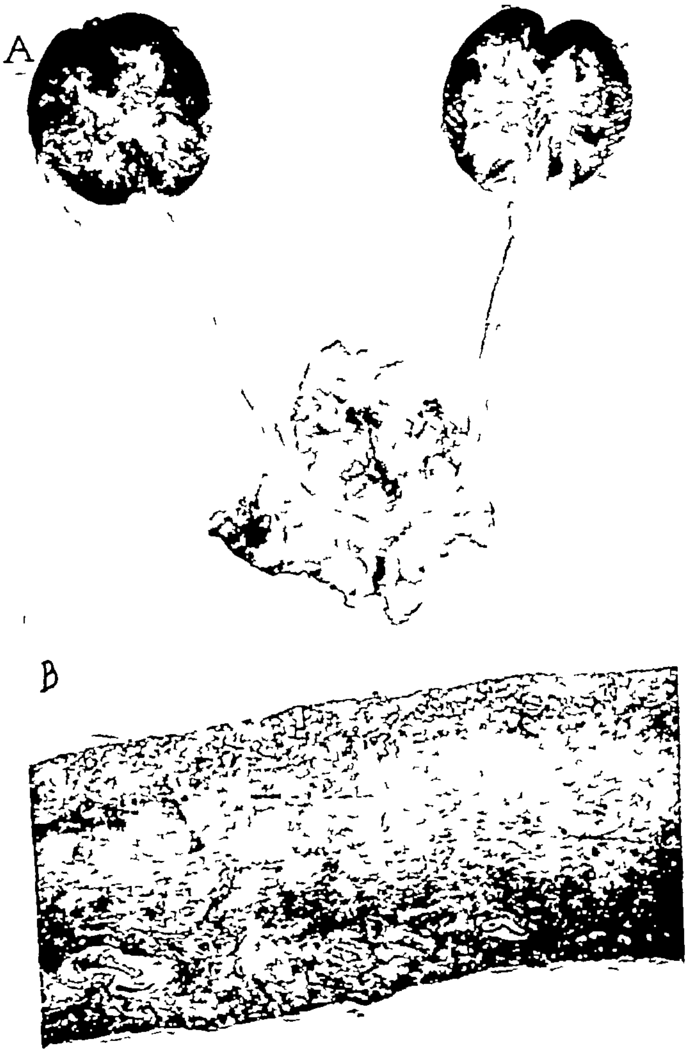

FIG 2 Case A G 4, postmortem specimen of regenerated bladder and kidneys *B*, microscopic section of regenerated bladder

Peripherally, there was an increasing amount of fibrous tissue which showed some collagenization No smooth muscle was seen except for questionable extension in the transitional zones between the ureters and the bladder and likewise between the urethra and bladder, however, this would be expected since in the dog experimental work, smooth muscle did not appear until after 70 days and the patient lived only fifty-three

N S was a 64-year-old man admitted to the hospital with known recurrent carcinoma of the bladder Cystoscopy revealed recurrent tumor extending from the vesical neck into the lumen of the bladder about 1 5 cm A biopsy showed

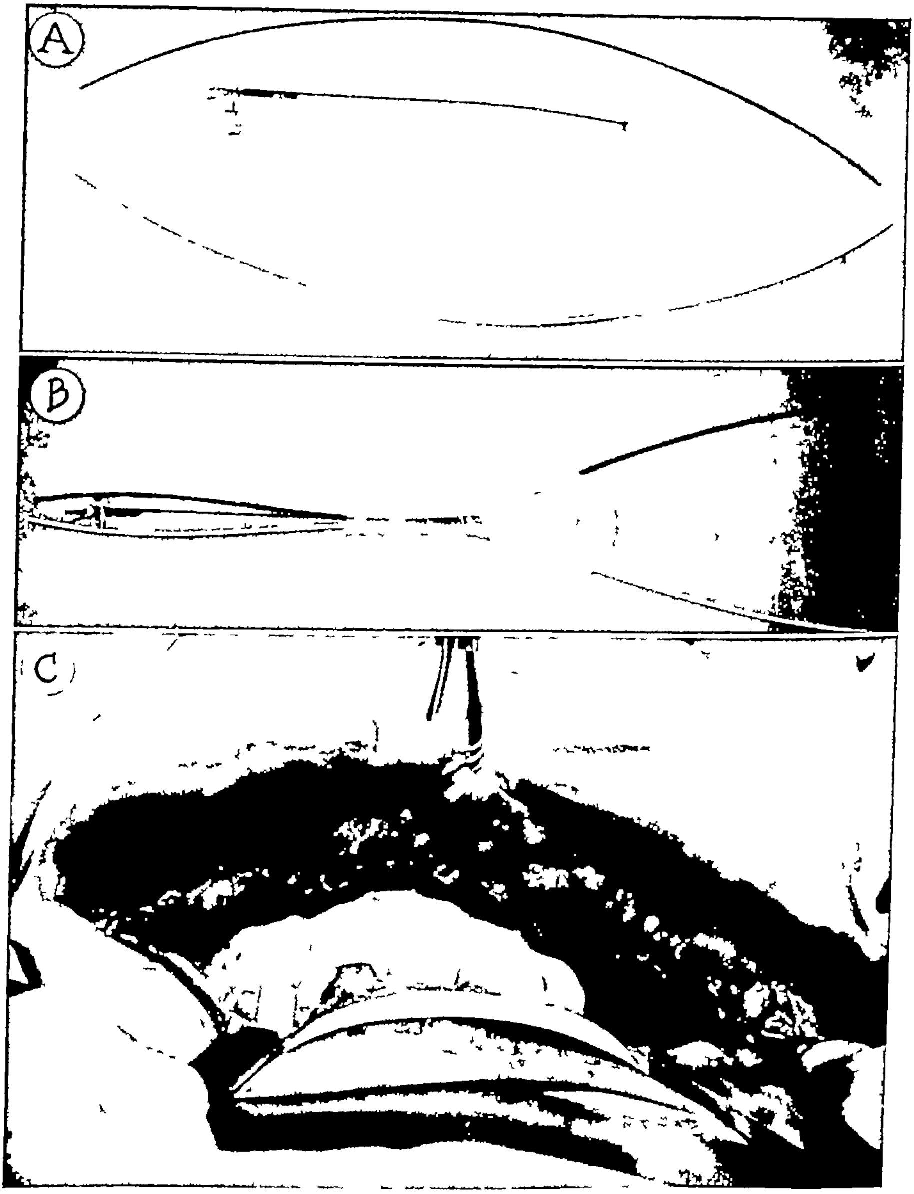

FIG 1 *A* and *B*, plastic mold, distensible bag and catheters *C*, plastic mold in place

gressing quite well until thrombophlebitis developed, and the patient expired 12 days after the second procedure from a pulmonary embolus

At autopsy, the regenerated urinary bladder was of fair size (fig 2, *A*) No epithelial lining was seen due to autolysis caused by a time delay in obtaining the post mortem (fig 2, *B*) The inner layers of the bladder were composed of granulation tissue which was exceedingly vascular and showed marked infiltration with lymphocytes, macrophages and occasional polymorphonuclear cells

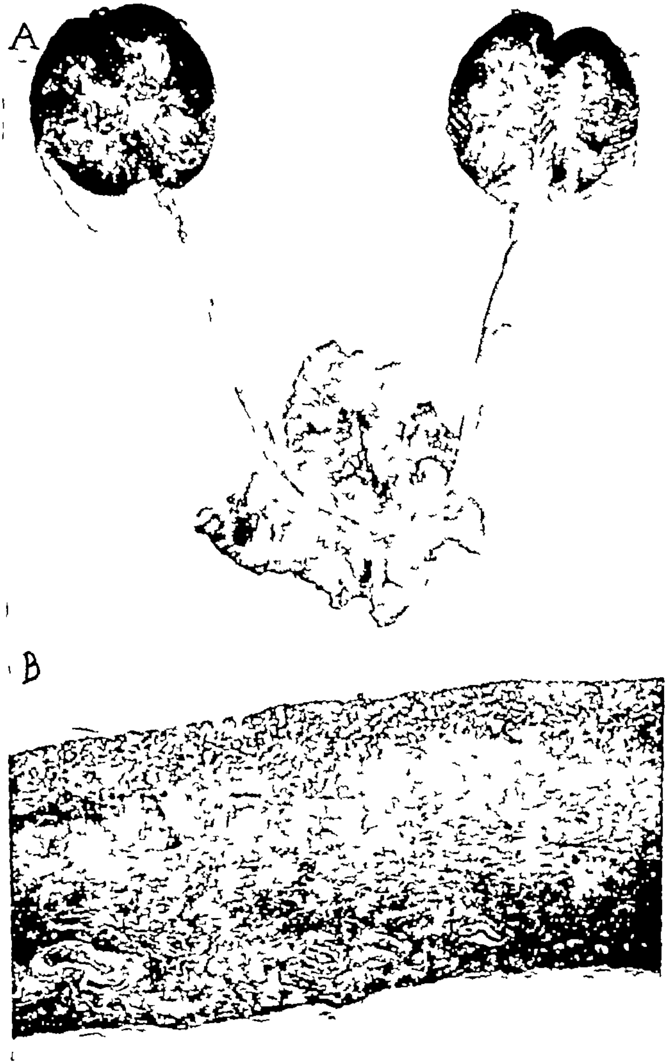

Fig 2 Case A G *A*, postmortem specimen of regenerated bladder and kidneys *B*, microscopic section of regenerated bladder

Peripherally, there was an increasing amount of fibrous tissue which showed some collagenization No smooth muscle was seen except for questionable extension in the transitional zones between the ureters and the bladder and likewise between the urethra and bladder, however, this would be expected since in the dog experimental work, smooth muscle did not appear until after 70 days and the patient lived only fifty-three

N S was a 64-year-old man admitted to the hospital with known recurrent carcinoma of the bladder Cystoscopy revealed recurrent tumor extending from the vesical neck into the lumen of the bladder about 1 5 cm A biopsy showed transitional cell carcinoma invading the muscularis Total prostatocystectomy with insertion of a plastic mold was performed January 27, 1955

During the postoperative course, right pyelonephritis developed followed by parenchymal abscesses with subsequent septicemia Death occurred February 21, twenty-five days postoperatively

At autopsy, a urinary pouch had regenerated around the plastic mold varying in thickness from 0 1 to 0 3 cm It showed evidence of granulation tissue being most prominent in the areas where the ureters were implanted These areas were reddish and the surfaces contained a small amount of purulent exudate, the remainder of the pouch being shiny and well preserved The wall showed the presence of vascular channels running throughout it Microscopically, the pouch was lined by granulation tissue covered with fibrin and infiltrated with polymorphonuclear leukocytes The wall was edematous and made up of inflamed, fatty tissue in which bands of collagen were seen interspersed No evidence of recurrence of carcinoma was found

K F was a 41-year-old woman with a long-standing history of interstitial cystitis and recurrent urinary tract infection The patient had been followed in our clinic since 1951 Response to bladder dilatations and silver nitrate instillations would give some symptomatic relief but only of short duration Cystograms showed bilateral ureteral reflux with marked dilatation of the entire upper tracts (fig 3, *A*) The bladder was small and contracted Subtotal cystectomy and insertion of a plastic mold were performed February 9, 1955

At present, 1½ years later, the patient is relatively asymptomatic Recurrent episodes of urinary infection continue A cystometrogram shows a straight line

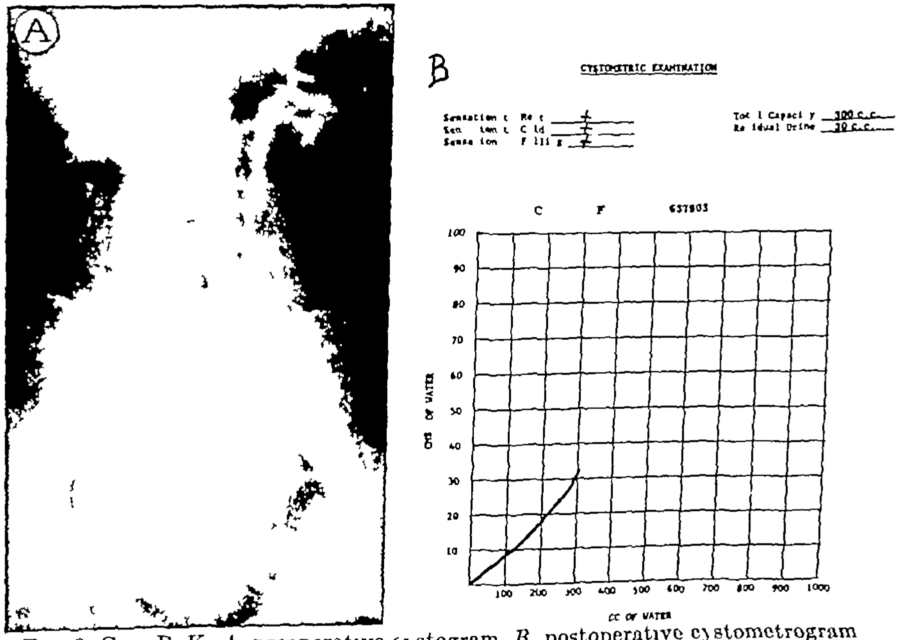

FIG 3 Case F K *A*, preoperative cystogram *B*, postoperative cystometrogram

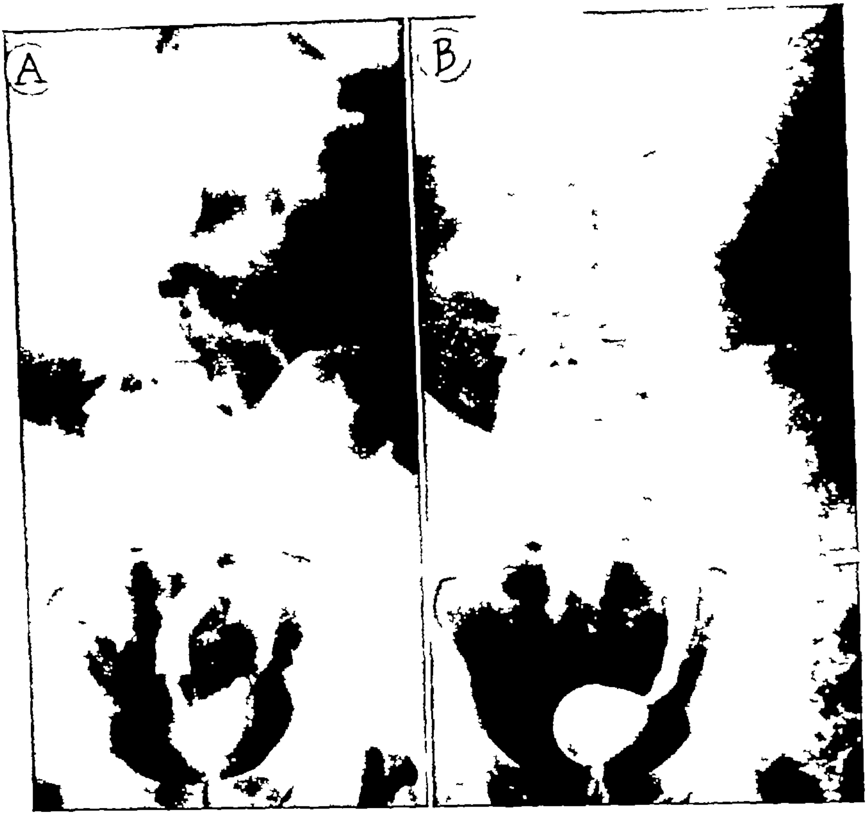

Fig 4 Case J S A preoperative cystogram *B* postoperative cystogram shows regenerated bladder and left ureteral reflux

curve with a 300 cc capacity and 30 cc residual urine (fig 3, *B*) Sensation was noted to heat, cold, and filling, but no pain was associated with distention The cystogram is normal but bilateral ureteral reflux with dilatation of the upper tract still persists

J S was a 55-year-old man who had a 30 year history of interstitial cystitis A suprapubic cystostomy had been performed in 1927 for a painful, contracted bladder A right nephrectomy for calculus-pyohydronephrosis was performed in 1939 The preoperative cystograms showed reflux on the remaining left side (fig 4 A)

A subtotal cystectomy with insertion of a bladder mold was performed February 24, 1955 Postoperatively there developed a vesicocutaneous fistula which necessitated excision At present, the patient is doing very well symptomatically, but renal function studies show a decrease to the point that it may be necessary to again divert the urinary stream in the future While there is adequate bladder capacity and the urinary stream is of good caliber and force, the postoperative cystogram still shows reflux up the remaining ureter (fig 4, *B*)

Z R a 59-year-old woman, had a history of urinary tract tuberculosis for 30

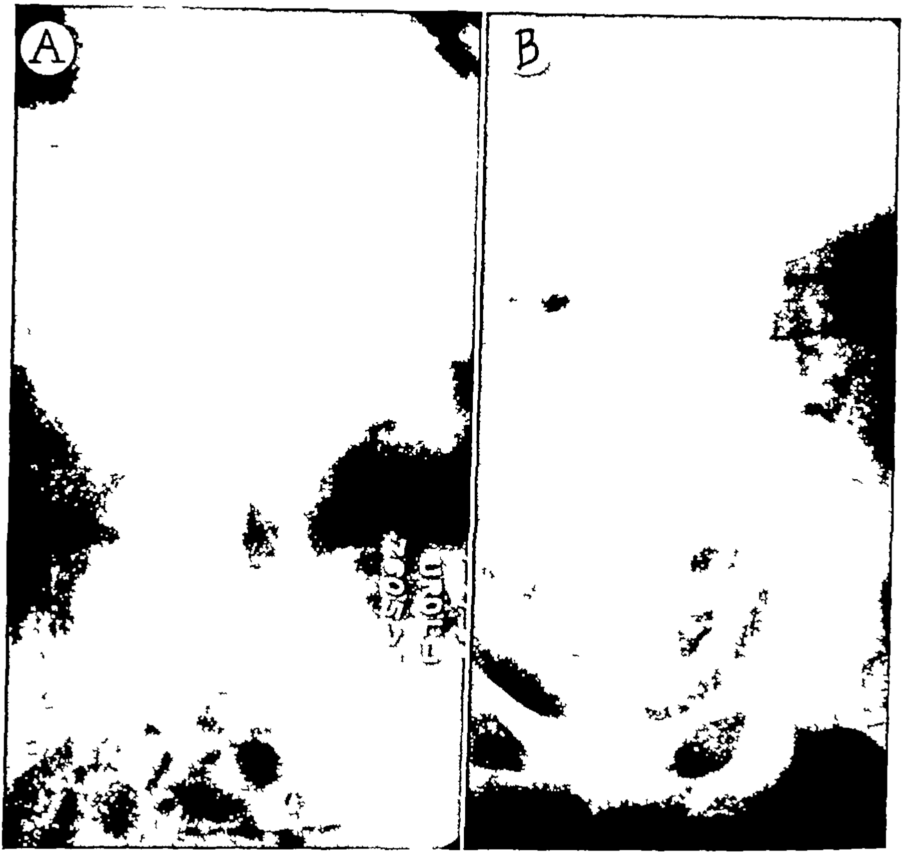

FIG 5 Case Z R *A*, injection of ureterostomy tube prior to surgery *B*, cystogram taken 9 months after subtotal cystectomy

years A right nephrectomy had been performed in 1923 for tuberculosis A left cutaneous ureterostomy was done in 1945 after several unsuccessful surgical attempts to close vesicovaginal and cervicovaginal fistulas Despite discouragement, an attempt at reconstruction of the urinary tract was insisted upon since life otherwise had become unbearable for the patient

Retrograde pyelograms revealed hydronephrosis with a large calculus in the lower pole of the kidney (fig 5, *A*) A calycectomy to remove this calculus was performed April 2, 1955 Two months later, the cutaneous ureterostomy was taken down and the insertion of a plastic mold was performed When the mold was removed 3 months later, no external sphincter control could be demonstrated Consequently, the regenerated bladder contracted down until at the last examinations the capacity was only 50 cc (fig 5, *B*) Thus bladder regeneration in this case was considered a failure

J W was a 53-year-old man with recurrent vesical tumors A transurethral resection of a solitary papillary transitional cell carcinoma had been done in June 1954 After the third recurrence, the patient was referred to our clinic for

FIG 6 Case J W Excretory urogram 3 months after total cystectomy

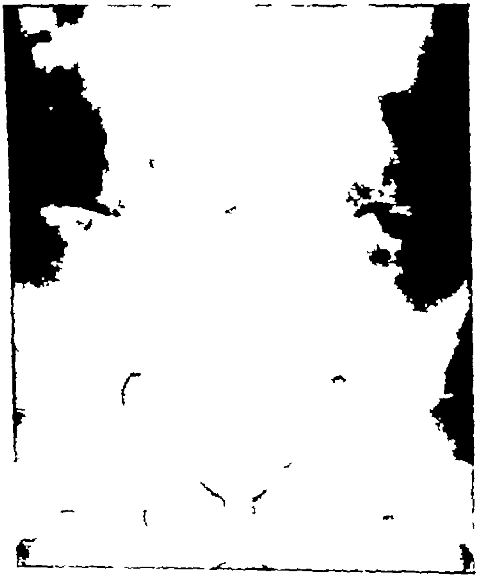

FIG 7 Case A M Cystogram 3 weeks after removal of plastic mold

a total cystectomy Cystoscopy at that time revealed a diffuse, sessile lesion involving the right posterior wall of the bladder The preoperative intravenous pyelograms were normal

Total cystectomy with insertion of the plastic mold was performed September 10, 1955 At the time of surgery, there was noted to be an indurated area of the right wall of the bladder, which seemed to be adherent to the lateral pelvic wall The pathological report revealed an undifferentiated carcinoma which had infiltrated the entire bladder wall

Intravenous pyelograms taken 3 months postoperatively revealed bilateral hydronephrosis (fig 6) By 6 months postoperatively, ureteral obstruction necessitated nephrostomies Later, intestinal obstruction required surgery at which time it was discovered there was widespread metastatic carcinoma The patient died approximately ten months after surgery No autopsy was obtained

A M was a 38-year-old man who had a 3 year history of recurrent vesical tumors Various surgical procedures and x-ray therapy had failed to rid him of his disease

Total cystectomy and insertion of a plastic mold were performed November 22, 1955 The pathology report revealed noninvasive transitional cell carcinoma When the mold was removed, the perineal urethrostomy failed to close, consequently, an indwelling catheter was left in the bladder A marked contraction of the bladder occurred When it was possible to remove the catheter, the bladder capacity improved slowly A cystogram at that time showed a good sized bladder capacity with bilateral reflux (fig 7)

Subsequently, a vesicocutaneous fistula developed and required excision and catheter drainage Later, right pyelonephritis that developed responded to antibiotics Due to persistence of the right recurring pyelonephritis, the patient consulted someone else, he subsequently has had bilateral ureterosigmoidostomy

SUMMARY

From the cases presented, we believe that regeneration of the urinary bladder does occur in humans A functioning reservoir develops provided intermittency of filling and emptying can be maintained after removal of the mold In those instances where continuous drainage is necessary, the reconstructed organ contracts to the extent that functional capacity is no longer maintained

Complications are prone to occur but by further study and better selection of cases, many of these may be overcome

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BLADDER NECK OBSTRUCTION AND ASSOCIATED LESIONS IN CHILDREN

EDGAR BURNS, EDWARD H RAY, Jr and JAMES W MORGAN
From the Department of Urology, Ochsner Clinic and Charity Hospital, New Orleans, La

Obstructive lesions of the lower urinary tract in children are now recognized as common Changes in the bladder and upper urinary tract are in proportion to the degree of obstruction and the length of time that it has existed Since these lesions are congenital, the duration of the obstruction is determined by the age of the child Associated lesions are frequently encountered

There is some variation of opinion as to the nature of the bladder neck lesion Reports of large series of patients treated surgically show that the obstruction is due to contracture of the internal vesical orifice in the majority of cases Other reports are devoted entirely to a discussion of congenital prostatic valves Still others raise the question as to whether or not there is an obstruction in many cases and attempt to explain the changes in the architecture of the urinary tract on the basis of segmental neurogenic maldevelopment In some of our own patients a definite reason for the changes found could not be determined, this suggests the possibility of atresia or failure of some part of the urinary tract to undergo normal development Therein lies the reason for meticulous study in each case as an individual problem so that appropriate management may be instituted

Of 129 children with congenital bladder neck obstruction treated surgically by us, the types of lesions and their distribution were as follows congenital prostatic valves in 3, congenital hypertrophy of the verumontanum in 2, and congenital hypertrophy of the internal sphincteric area in 123 The remaining patient had a greatly dilated urinary tract when examined at the age of 6 weeks An obstructive lesion in this case was questionable and failure of normal development appeared more likely From our experience it would appear that the frequency of bladder neck obstruction due to congenital prostatic valves has been overemphasized This has also been the observation in other medical centers where a large number of urologic problems in children is seen

Congenital hypertrophy of the verumontanum will be encountered rarely but it must be considered in the examination of males in order that it may not be overlooked either as an associated lesion or as the primary cause of the obstruction In our 123 cases of obstruction due to hypertrophy of the internal vesical area the distribution according to sex was approximately the same The hypertrophic process may extend into the trigone in both sexes and in males it may involve the prostate so that the cystoscopic appearance is that of miniature prostatic hypertrophy

In the study of the cases considered in this review a careful neurologic examination was done and those cases with neurogenic lesions, with the exception of one

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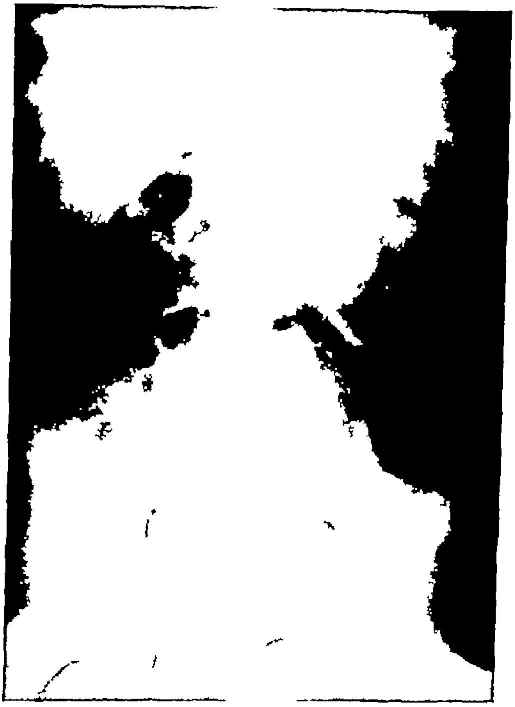

FIG 1 Roentgenogram of boy 4 years old with meningomyelocele and disturbance of nerve fibers supplying the detrusor muscle with those to the sphincter chiefly intact

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Changes in the urinary tract produced by bladder neck obstruction in children vary somewhat from those observed in adults The period during which hypertrophy of the bladder musculature may compensate for the increased difficulty in performing its function appears to be short in children, giving way to such rapidly progressive dilatation that the bladder becomes a large atonic sac Vesicoureteral reflux is also encountered more frequently in children In those patients with reflux varying degrees of hydronephrotic atrophy of the renal cortex will be found Vesical diverticula of clinical significance, on the other hand, occur less frequently in children They were found in only 2 of our 129 cases If the obstruc-

tion is complicated by infection, the secondary obstructive changes will progress at a more rapid rate Like bladder neck obstruction in the older age group, early recognition is important

SYMPTOMATOLOGY

The signs and symptoms produced by bladder neck obstruction in children are subject to wide individual variation Perhaps the most common finding that leads to investigation of the urinary tract is pus in the urine Infected urine was found in 79 per cent of our cases and 89 per cent of these had suffered recurrent attacks of chills and fever It should be emphasized that infection in these cases is a complication of obstruction, frequently a late one, and the fact that urinary infection led to the initial urologic investigation indicates that earlier symptoms were overlooked or considered insignificant Importance should therefore be attached to any variation from the normal voiding pattern in a child

Other symptoms noted in our records are frequency and straining to urinate, urgency, enuresis, overflow incontinence, acute retention and hematuria Frequency and straining to urinate are perhaps the earliest symptoms and may be observed during the first few months of life Since crying is the child's only means of expressing discomfort at this age, abnormalities in the voiding pattern that are detected during this period are based largely upon objective signs rather than subjective evidence Enuresis is the most common urinary disturbance in children It is functional in the majority of cases, and urologic investigation for enuresis alone is not usually carried out in children under the age of 4 years The reason for this is that many children do not quit wetting the bed until that age or even later Slightly more than 28 per cent of children who were brought to us because of enuresis had some type of obstructive lesion of the lower urinary tract producing vesical irritability Some of these had had medical treatment and psychotherapy before attention was directed to the urinary tract On the basis of our experience it appears that a safer course to follow would be to consider enuresis after the age of four years as a symptom of possible urologic disease rather than a functional disturbance If there are other associated disturbances in bladder function before that age, investigation should not be delayed Recognition of organic disease in this group during a period when the urinary tract may be restored to normal always justifies such study The ease with which urologic investigation can be carried out in children at the present time has largely removed objections to such examination Wetting the clothing during the day time is of more significance than enuresis and rarely occurs in the absence of urologic disease

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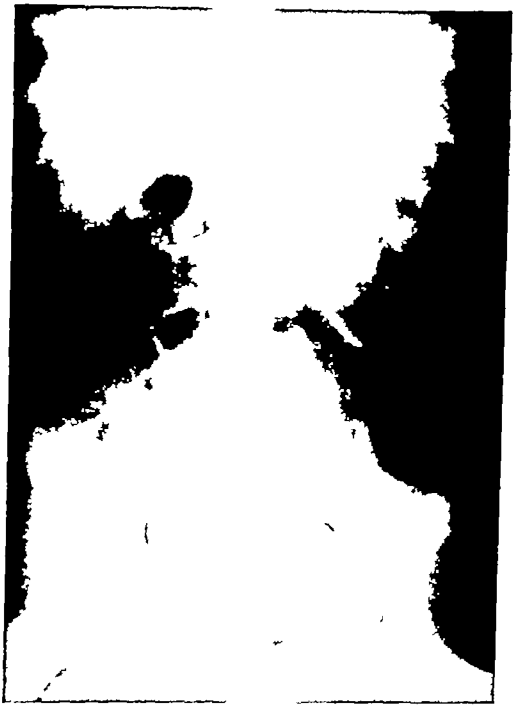

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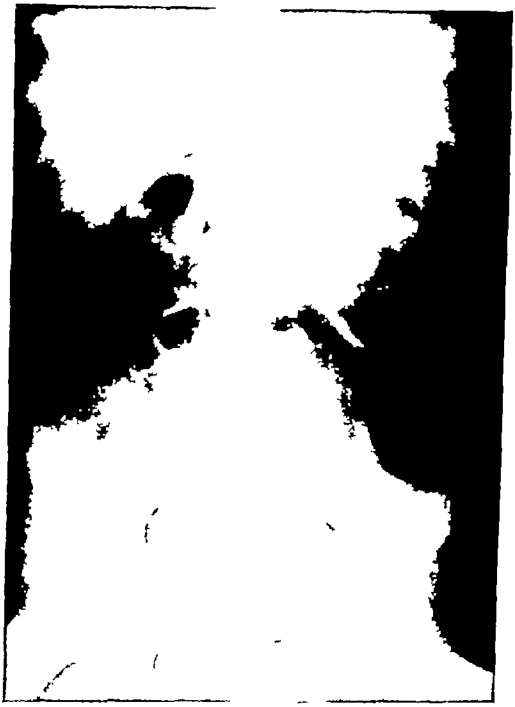

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Another example is that of a 5-year-old girl whose first urologic examination was prompted by a cerebrovascular accident The urologic study was done as a part of the investigation to determine the cause of hypertension Atrophic pyelonephritis was found on the right side and was the result of chronic infection of the urinary tract secondary to bladder neck obstruction

DIAGNOSIS

The diagnosis of obstruction of the lower urinary tract in children is easy to make Chemical and bacteriologic studies of the urine and renal function tests are routine procedures Specific urologic studies include excretory urography, retrograde cystography, cystoureteroscopic examination and retrograde pyelo ureterography, as indicated

The excretory urogram will provide information regarding renal function and will frequently show variation from the normal that may be produced by an obstructive lesion It will also indicate other associated anomalies of the urinary tract, if present In the majority of children excretory urography can be accomplished by the intravenous administration of a contrast medium In infants the medium may be injected intramuscularly Addition of hyaluronidase to the medium to hasten absorption has been suggested, and we have tried this in the past Its use, however, may be associated with serious complications If the site of the injection is not adequately sterilized, bacteria may be carried into the tissue, and with the aid of hyaluronidase, may produce widespread cellulitis I have seen one infant die from widespread cellulitis which was attributed to use of hyaluronidase in this way Diagnostic urograms can be obtained without it

Retrograde cystography is the most important of the urographic studies It will provide information regarding the location of the obstruction and sometimes will indicate the nature of the lesion itself, that is, whether the obstruction is at the apex of the prostate from congenital valves at the internal vesical orifice, from contracture or from hypertrophy of the verumontanum In addition, it will outline the size and architecture of the bladder and indicate whether or not vesicoureteral reflux is present The practical value of a delayed cystogram to demonstrate reflux not shown on the original film is questionable Cystography is performed by filling the bladder through a catheter from the barrel of a 2 ounce Triumph syringe held only the length of the catheter above body level The solution is allowed to flow by gravity and *should never be forcefully injected*

These combined urographic studies may provide the required information for treatment in many cases Nevertheless, they should be supplemented by cystourethroscopic examination in all cases This procedure provides a means of calibrating the urethra to rule out other congenital obstructive lesions, such as stricture and especially congenital stenosis of the external urethral meatus It should be remembered that stenosis of the meatus is a common finding that

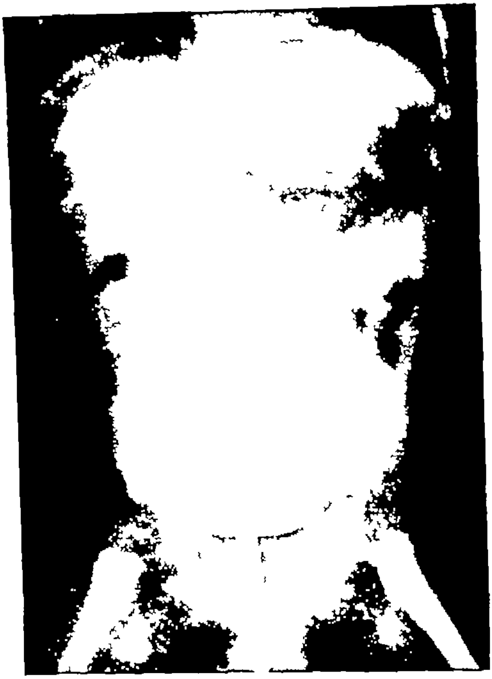

FIG 2 Roentgenogram of boy 4 months old with stenosis of external urethral meatus with beginning vesicoureteral reflux on the left side

occurs with equal frequency in males and females It may occur independent of other lesions and be obstructive enough to produce signs of back pressure, and if unrecognized, may lead to renal failure (fig 2)

For the sake of comfort of the patient and accuracy of the study all instrumental examinations in children should be done with the use of a general anesthetic It is our custom to instill a solution of sodium pentothal into the rectum, and in many of the younger children this is sufficient It may be supplemented by nitrous oxide if necessary

By correlation of the findings obtained from combined diagnostic studies the indications for treatment are usually clear Cases fall roughly into several groups 1) those that require only removal of the primary obstructive lesion, 2) those in which removal of the obstruction and plastic procedures on one or both ureters for vesical ureteral reflux are indicated, 3) those with extensive damage to the upper urinary tract in which removal of the obstruction should be followed by a long period of drainage, and 4) those with associated lesions, such as stenosis of the external urethral meatus, ureterocele or ureterovesical junction obstruction, that can be corrected at the same time

TREATMENT

Treatment of bladder neck obstruction in children is surgical removal of the primary lesion supplemented by whatever procedure is indicated in the individual case In females, if the obstruction is of borderline significance, urethral dilatation under anesthesia may be tried The usual finding in this group with questionable obstruction is either enuresis or recurrent infection of the urinary tract Considerable judgment is required, however, to select the case for such treatment and to determine the extent to which it is to be carried out It is doubtful that urethral dilatation should ever be performed for a borderline lesion in the male The danger of injuring the urethral mucosa with subsequent stricture formation is considerable, and there would be little consolation in creating one type of obstruction while treating another

The method by which the primary obstructive lesion is removed surgically is a matter of individual choice The two widely used methods are transurethral resection and the suprapubic transvesical approach Selection of the approach to be used depends to a great extent upon the age of the patient For the transurethral approach the urethra must be large enough to accommodate an instrument of sufficient size for the lens to provide adequate vision and a working element large enough to remove the obstruction Most children less than four years of age, especially boys, will not lend themselves well to transurethral resection Use of perineal urethrostomy in males will not eliminate the likelihood of producing injury to the membranous urethra It is in this group of children that the suprapubic transvesical approach has been widely used during the past 10 years On our service the obstruction was previously removed by a liberal wedge resection of the posterior internal vesical area In the more recent cases wedge resection has been supplemented by a modification described by Young in 1953 By this modification a longitudinal incision is made through the anterior internal vesical orifice and closure is carried out in a transverse manner This provides a perceptible increase in the diameter of the internal vesical orifice

Transurethral resection is quite adequate for removal of the obstruction in older children Some urologists use it for all age groups and appear to be satisfied with the results obtained In our hands, better results have been obtained by the open approach in the younger age group

In the treatment of those patients with vesicoureteral reflux, decision must be made between 1) removal of the primary obstructive lesion alone, 2) removal of the obstruction with reimplantation of one or both ureters, and 3) removal of the obstruction with prolonged drainage by indwelling urethral catheter or suprapubic cystostomy In those patients with early dilatation of the upper urinary tract treated by removal of the obstruction alone, interval examination is important in order to be certain that there is progressive improvement In the second group the period of reflux will be shortened if the ureters are severed at their entrance into the bladder and reimplanted into a different position This can be done at the same time the bladder neck obstruction is removed Selection of cases for treatment in this manner is a matter of judgment The third group is made up of those cases with severe decompensation of the upper urinary tract and varying degrees of hydronephrotic atrophy of the renal cortex Such cases require prolonged drainage in order to offer a maximum opportunity for a return to normal In females drainage can be accomplished by indwelling urethral catheter In males, however, suprapubic cystostomy is required because of the

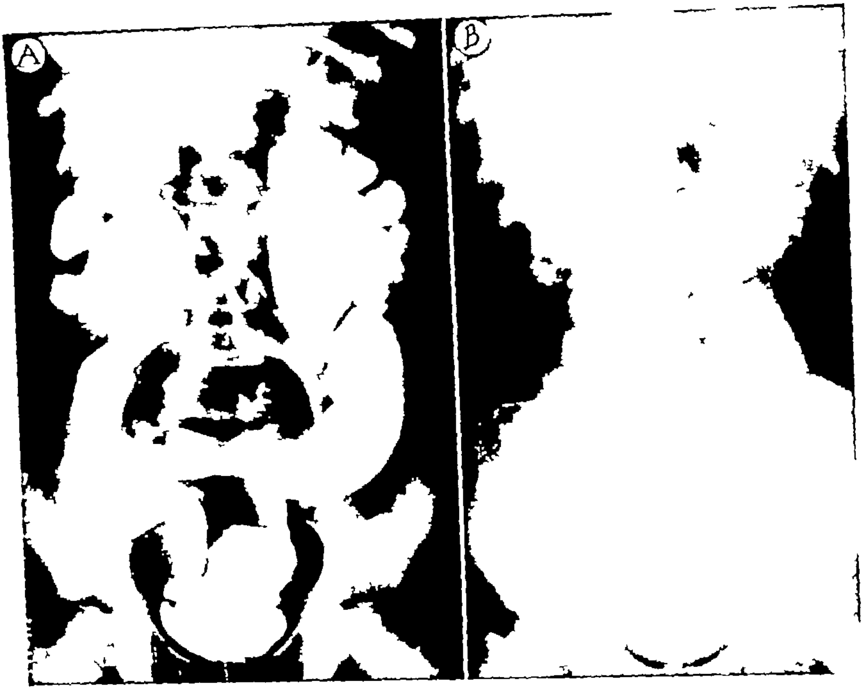

FIG 3 A, roentgenogram of girl 4 years old with bladder neck obstruction and decompensated urinary tract B, roentgenogram of same child after transurethral indwelling catheter drainage for 6 months

tendency to development of periurethral abscesses and urethral stricture A small plastic collecting bag is attached to the clothing and worn without particular inconvenience Surprising improvement is sometimes obtained in the presence of of apparently irreversible changes (fig 3)

In cases of long standing ureteral reflux the ureters have a tendency to become elongated and tortuous The tortuosity in some cases may be obstructive to the passage of urine from the kidneys to the bladder Resection of the tortuous areas is required as a part of the reconstructive procedures In planning resection of such ureters the surgeon should remember that they are thin walled and only the obstructive area should be disturbed There is not enough intrinsic blood supply to maintain viability, and extensive freeing of the ureter from its bed may lead to slough This procedure was accomplished bilaterally in 2 of our cases The installment emptying of the dilated bladder with or without the aid of manual compression is a dangerous practice and can lead only to progressive renal failure if carried out for a prolonged period

Congenital obstructive lesions located at the intramural portion of the ureters and ureteroceles that are encountered in patients with bladder neck obstruction can be corrected surgically at the same time the bladder neck lesion is removed In the case of each type the ureter should be cut and reimplanted into a different position In the case of ureterocele, if there is severe dilatation of the ureter above ureteral reflux will follow simple resection of the cyst In the case of

intramural stricture, ureteral reflux will always follow ureteral meatotomy if adequate meatotomy has been performed It has been found in all patients observed on our service who had had ureteral meatotomy It is recognized that continued ureteral reflux will contribute to renal damage Reimplantation of the ureter, on the other hand, should be followed by a good result if all the fundamental rules of plastic surgery are observed

SUMMARY

Obstructive lesions of the urinary tract in children are common They are congenital and often associated with other abnormalities Three types are encountered congenital prostatic valves, congenital hypertrophy of the verumontanum and, most commonly, congenital hypertrophy of the internal sphincteric orifice

The clinical manifestations vary considerably The commonest finding is pyuria Other manifestations are frequency and straining to urinate, urgency, enuresis, overflow incontinence, acute retention and hematuria

The diagnosis of obstruction of the lower urinary tract in children is easy to make In addition to routine chemical and bacteriologic studies of the urine and renal function tests, specific urologic studies should be done when indicated These include excretory urography, retrograde cystography, cystoureteroscopic examination and retrograde pyelo-ureterography

Treatment of bladder neck obstruction in children is surgical removal of the primary obstructive lesion supplemented by the appropriate procedure for associated lesions when present This may be accomplished by transurethral resection or through the suprapubic transvesical approach

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YOUNG, B W Retropubic approach to vesical neck obstruction in children Surg, Gynec & Obst, 96 150-154, 1953

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LOCAL INJECTIONS OF HYDROCORTISONE FOR THE EFFECTIVE TREATMENT OF CIRCUMSCRIBED STRICTURES OF THE URETHRA

MELVIN K. LYONS AND CHARLES D. BONNER

From the Cancer Research and Cancer Control Unit of the Department of Surgery, Tufts University School of Medicine, the Department of Urology, Boston University School of Medicine and the Department of Urology, Beth Israel Hospital, Boston, Mass.

In July 1955 Bonner et al. reported preliminary observations made in a group of 18 cases of urethral and meatal strictures which were treated by the local injection of hydrocortisone. The rationale for the use of this method was the outgrowth of the observation made by one of us (C. D. B.) on the resolving effect of hydrocortisone following its injection into scar and fibrous tissue seen in contracted tendons of spastic hemiplegic and paraplegic patients. It was also based on reports found in the literature suggesting an inhibitory effect upon fibroblastic proliferation by hydrocortisone in experimental animals as well as a possible lytic effect on scar tissue in humans with Peyronie's disease.

The necessity for a relatively simple, inexpensive but satisfactory method for the treatment of strictures is well known. A number of methods have been used over the years—none of which has fulfilled the above prerequisites. These were detailed in our original report. In spite of these methods, strictures of the urethra and meatus have continued to be a major therapeutic problem in urology. Even though the frequency of gonorrheal strictures has decreased since chemotherapy and antibiotics came on the scene, more and more strictures are being seen postoperatively and following instrumentation of the urethra.

It is believed that the following method fits the need outlined above and will give nearly 100 per cent results in simple circumscribed strictures of the urethra or meatus.

METHOD

Fifty-three consecutive patients harboring 56 strictures of the urethra and meatus were studied (table 1). These included 18 strictures of the meatus, 15 strictures of the anterior urethra, 18 strictures of the membranoprostatic junction and 5 strictures of the posterior urethra. In all instances, the caliber of the urethra at the site of the stricture was measured with the aid of standard urological instruments before treatment and recorded in terms of the usual French size as used by urologists.

An aqueous suspension of hydrocortisone was injected directly into the tunica propria at the base of the stricture at two clock positions, five and seven or three

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Read at annual meeting, American Urological Association, Boston, Mass., May 31, 1956.

Supported in part by funds from an institutional grant of the American Cancer Society, Incorporated.

The material used in this study was contributed by Merck & Company, Rahway, New Jersey, Sharpe and Dohme Company, Philadelphia, and the Upjohn Company, Kalamazoo, Michigan.

The endoscopic needle was developed and manufactured with the assistance of Mr. F. J. Wallace and Mr. Joseph Held of American Cystoscope Makers, Inc., New York, N. Y.

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34	A A	75	M	Anterior urethra	Traumatic	6 yrs	3	75 5	Filiform	20F	Every 2-4 wks	0	13	Excellent	No clinical evidence of stricture
35	I B	71	M	Membranoprostatic junction	Traumatic	6 yrs	2	50 0	11F	20F	Every 4 wks	0	11	Excellent	No clinical evidence of stricture
36	D I	50	M	Meatus	Inflammatory	6 yrs	2	50 0	18F	30F	Every 2 wks	0	10	Excellent	No clinical evidence of stricture
37	C W	71	M	Meatus	Transurethral resection	(New)	2	50 0	10F	30F	None	0	9	Excellent	No clinical evidence of stricture
38	W R	31	M	Meatus	Unknown	(Newly discovered)	1	25 0	16F	28F	None	0	8	Excellent	No clinical evidence of stricture discovered at cystoscopy for infertility study
39	H W	61	M	Meatus	Transurethral resection	(New)	3	75 0	10F	30F	None	0	8	Excellent	No clinical evidence of stricture
40	A M	16	M	Membranoprostatic junction	Unknown	(Newly discovered)	2	75 0	16F	28F	None	0	8	Excellent	No clinical evidence of stricture
41	I M	75	M	Membranoprostatic junction	Transurethral resection	(New)	3	75 0	Filiform	28F	None	0	7	Excellent	No clinical evidence of stricture
42	P O	23	M	Meatus	Transurethral resection	(New)	2	50 0	Filiform	28F	None	0	7	Excellent	No clinical evidence of stricture
43	J D	43	M	Membranoprostatic junction	Unknown	(Newly discovered)	1	50 0	16F	20F	None	0	6	Excellent	No clinical evidence of stricture
44	W H	70	M	Meatus	Transurethral resection	(New)	2	100 0	10F	24F	None	0	6	Excellent	No clinical evidence of stricture
45	H S	60	M	Membranoprostatic junction	Gonorrhea	15 yrs	3	75 0	Filiform	28F	Every 8 wks	0	6	Excellent	No clinical evidence of stricture
46	R G	65	M	Meatus	Transurethral resection	(New)	3	75 0	11F	20F	None	0	6	Excellent	No clinical evidence of stricture
47	G B	51	M	Membranoprostatic junction	Gonorrhea	30 yrs	1	87 5	Filiform	20F	Every 4 wks	0	1	Excellent	No clinical evidence of stricture
48	W H	60	M	Anterior urethra	Traumatic	50 yrs	3	75 0	Filiform	28F	Every 2-4 wks	0	1	Excellent	No clinical evidence of stricture
49	H C	70	M	Meatus	Transurethral resection	(New)	2	50 0	10F	28F	None	0	2	Excellent	No clinical evidence of stricture
50	D G	18	M	Anterior urethra	Gonorrhea	20 yrs	1	25 0	Filiform	24F	Sporadic	0	2	Excellent	No clinical evidence of stricture
51	R B	38	M	Anterior urethra	Gonorrhea	11 yrs	1	75 0	Filiform	28F	Every 4 wks	0	2	Excellent	No clinical evidence of stricture

Summary of Unsuccessful Cases

1	I B	30	M	Anterior urethra	Congenital and traumatic	30 yrs	3	75 0	Filiform	Filiform	Sporadic	sporadic	10	Poor	Multiple strictures of urethra finally submitted to internal urethrotomy and injection of lines of incision
2	J K	70	M	Posterior urethra	Traumatic	5 yrs	2	50 0	Filiform	12F	Every 2 wks	More surgery	18	Poor	Thick vesical neck contracture Patient had false urethral passage which was ruptured by traumatic passage of catheter 24 hours after second injection Surgical intervention took place
3	A A	75	M	Membranous and posterior	Traumatic	6 yrs	7	225 0	Filiform	24F	Every 2 wks	Every 4 to 6 wk	15	Fair	Multiple anterior and posterior urethral strictures resulting from repeated instrumentations for bladder stone crushing
4	D I	50	M	Anterior urethra	Inflammatory	6 yrs	7	125 0	Filiform	16F	Every 2 wks	Every 4 to 6 wk	0	Fair to Poor	Multiple strictures of urethra finally submitted to internal urethrotomy and injection of lines of incision Now calibrates to 20F with ease and has excellent stream
5	J K	15	M	Anterior urethra	Gonorrhea	10 yrs	3	150 0	18F	20F	Every 4 wks	Every 8 to 10 wk	0	Poor	Elongated area of stricture Should be submitted to internal urethrotomy

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* Deceased

TABLE 1

Summary of Successful Cases

Case No	Patient	Age	Sex	Site of Stricture	Cause	Duration of Stricture	No of Injections	Total Dose	Caliber of Stricture		Frequency of Dilatation		Duration Follow up Study	Result	Remarks
									Before Therapy	After Therapy	Before Therapy	After Therapy			
		yr						mg					mo		
1	G C	60	M	Meatus	Transurethral resection	(New)	3	37.5	20F	26F	None	0	30	Excellent	No clinical evidence of stricture
2	H T	30	M	Membranoprostatic junction	Gonorrhea	10 yrs	3	37.5	Filiform	24F	Every 2-4 wks	0	28	Excellent	No clinical evidence of stricture
3	H J	72	M	Meatus	Transurethral resection	(New)	8	137.5	16F	26F	None	0	28	Excellent	No clinical evidence of stricture
4	B B	42	M	Posterior urethra	Gonorrhea	25 yrs	3	37.5	Filiform	26F	Weekly	0	28	Excellent	Therapy followed internal urethrotomy, catheter left in urethra for 2 days before operation
5	W E	60	M	Meatus	Transurethral resection	(New)	2	50.0	16F	26F	None	0	27	Excellent	No clinical evidence of stricture
6	H H	70	M	Anterior urethra	Gonorrhea	(Newly discovered)	2	25.0	Filiform	26F	None	0	25	Excellent	No clinical evidence of stricture
	P S	28	M	Anterior urethra	Traumatic	8 yrs	5	137.5	16F	26F	Every 2-6 wks	0	25	Excellent	Stricture developed after repair of hypospadias with mucosal graft no clinical evidence of stricture
8	M M	65	M	Anterior urethra	Gonorrhea	(Newly discovered)	1	25.0	Filiform	26F	None	0	24	Excellent	No clinical evidence of stricture
9	V P	40	M	Anterior urethra	Gonorrhea	11 yrs	2	50.0	Filiform	24F	Every 2 wks	0	24	Excellent	No clinical evidence of stricture
10	D J	66	M	Anterior urethra	Traumatic	3 yrs	3	75.0	18F	30F	Every 24 dys	1	15*	Excellent	One dilation done because patient thought urinary stream was slowing up sound inserted easily stricture soft
11	M M	53	F	Meatus	Inflammatory	2 yrs	3	50.0	18F	28F	Every 2-4 wks	0	21	Excellent	No clinical evidence of stricture
12	S L	74	M	Anterior urethra	Gonorrhea	3 yrs	1	25.0	Filiform	22F	Every 2-12 wks	0	21	Excellent	No clinical evidence of stricture
13	C N	17	M	Meatus	Transurethral resection	3 yrs	3	75.0	Filiform	26F	None	0	22	Excellent	No clinical evidence of stricture
14	S T	62	M	Meatus	Transurethral resection	(New)	2	50.0	14F	26F	None	0	21	Excellent	No clinical evidence of stricture
15	E C	82	M	Meatus	Transurethral resection	(New)	3	75.0	12F	26F	None	0	21	Excellent	No clinical evidence of stricture
16	F W	67	M	Meatus	Transurethral resection	(New)	2	50.0	14F	24F	None	0	21	Excellent	No clinical evidence of stricture
17	H K	58	M	Meatus	Transurethral resection	(New)	3	75.0	Filiform	26F	None	0	21	Excellent	No clinical evidence of stricture
18	J M L	81	M	Meatus	Transurethral resection	(New)	2	50.0	10F	24F	None	0	20	Excellent	No clinical evidence of stricture
19	N F	78	M	Membranoprostatic junction	Suprapubic prostatectomy	5 yrs	3	75.0	Filiform	26F	Every 1-2 wks	0	18	Excellent	No clinical evidence of stricture
20	J K	40	M	Membranoprostatic junction	Traumatic	5 yrs	2	50.0	Filiform	28F	Every 2-4 wks	0	18	Excellent	No clinical evidence of stricture
21	A V	62	M	Membranoprostatic junction	Transurethral resection	9 yrs	3	75.0	Filiform	28F	Every 4 wks	0	16	Excellent	No clinical evidence of stricture
22	A V	62	M	Posterior urethra (vesical neck)	Transurethral resection	9 yrs	2	50.0	16F	28F	Every 1 wks	0	10	Excellent	No clinical evidence of stricture
23	S B	60	M	Membranoprostatic junction	Perineal prostatectomy	(New)	2	50.0	Filiform	26F	None	0	15	Excellent	No clinical evidence of stricture
24	F M	75	M	Anterior urethra	Gonorrhea	11 yrs	2	50.0	20F	28F	Every 4 wks	0	15	Excellent	No clinical evidence of stricture
25	C P	68	M	Posterior urethra	Suprapubic prostatectomy	(New)	3	100.0	Filiform	24F	None	0	15	Excellent	No clinical evidence of stricture
26	A E	72	M	Membranoprostatic junction	Transurethral resection	(New)	2	50.0	Filiform	28F	None	0	15	Excellent	No clinical evidence of stricture
27	H S	66	M	Membranoprostatic junction	Perineal prostatectomy	(New)	2	100.0	Filiform	28F	None	0	15	Excellent	No clinical evidence of stricture
28	C S	63	M	Membranoprostatic junction	Gonorrhea	5 yrs	2	50.0	Filiform	24F	Every 4 wks	0	15	Excellent	No clinical evidence of stricture
29	I P	63	M	Membranoprostatic junction	Inflammatory	12 yrs	2	50.0	24F	28F	Sporadic	0	11	Excellent	No clinical evidence of stricture striking symptomatic relief
30	J R	37	M	Anterior urethra	Gonorrhea	10 yrs	3	150.0	Filiform	28F	Every 2-4 wks	0	11	Excellent	No clinical evidence of stricture
31	N T	40	M	Membranoprostatic junction	Transurethral resection	(New)	3	125.0	Filiform	28F	None	0	13	Excellent	No clinical evidence of stricture
32	N T	40	M	Posterior urethra	Transurethral resection	(New)	3	125.0	Filiform	28F	None	0	13	Excellent	No clinical evidence of stricture
33	C O	77	M	Membranoprostatic junction	Suprapubic prostatectomy	(New)	3	112.5	Filiform	28F	None	0	13	Excellent	No clinical evidence of stricture

urological problem provided the original stimulus leading to this method of therapy In 1947 this 66-year-old man from North Carolina underwent suprapubic prostatectomy in Boston followed in 1949 by local resection of a bladder carcinoma and the implantation of radon Subsequently many cystoscopies were required and a stricture developed in the anterior urethra which was dilated with difficulty every 24 days Because of the pain endured with each dilatation and presence of a false passage which caused understandable difficulties to doctors in his home state the patient came to Boston every 24 days for dilatation by the urologist who had operated upon him This necessitated monthly expenses for transportation and hospitalization in addition spinal anesthesia had to be given the urethra had to be dilated cystoscopy had to be performed and persistent urinary tract infections had to be treated This costly routine had lasted 3 years

It was shortly after the patient's monthly hospital sojourn in November 1953 that one of us (C D B) injected hydrocortisone into the shortened fibrotic Achilles tendon of a young woman with a spastic hemiparesis of several years' duration due to a cerebral embolus All conventional methods of physical therapy had failed to stretch this tendon Two days after the first injection of 5 cc of hydrocortisone into this tendon it became soft and distensible Following the second injection the tendon stretched to its normal length This striking softening of connective tissue by hydrocortisone suggested the use of this procedure in urethral and meatal strictures Nine successful cases were done and with that evidence the patient's urologist permitted us to try the new method in June 1954 during the patient's last hospital admission

On June 16 1954 the caliber of urethra was 18F and was dilated with difficulty to 28F Cystoscopy and additional radon implantation were done Three days following this dilatation the stricture had narrowed to 22F and was re-dilated with difficulty to 28F after the injection of 12 5 mg hydrocortisone at two sites Two days later the stricture was soft and the urethra was easily dilated to 30F The second treatment was given On June 23 the stricture was no longer noticeable and the caliber of urethra was still 30F After the third injection the patient did well for a month when complete urinary obstruction developed A urologist in his home town passed a sound easily and found no evidence of stricture The urethra had been occluded by a piece of eschar from the site of radon implantation floating in the bladder The removal of this corrected the urinary obstruction

About 9 weeks after treatment the patient felt that his urinary stream was slowing down but dilatation was easily accomplished There was no evidence of constriction Since that time the patient was seen at intervals for cystoscopies which were now done easily in the urologist's office From March 1955 until he expired in January 1956 the patient was bedridden and in the terminal stages of metastasizing cancer During this time constant drainage was maintained and the catheter changed about once a week There were no further difficulties with catheter passage and the stricture remained open

Case 23 This 69-year-old man was admitted for treatment of a stricture at the junction of the membranous and prostatic portions of the urethra which had resulted from a perineal prostatectomy done in 1954 Initial calibration revealed

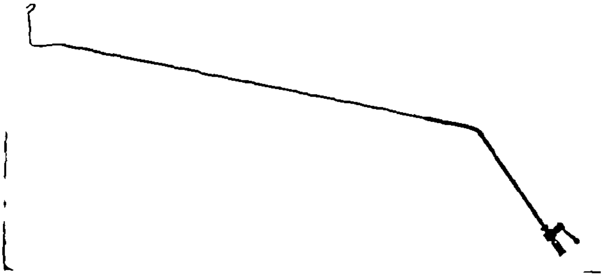


FIG 1 Needle used for injection of urethral strictures Main features are its length and rigidity Points are replaceable *Needle obtainable from American Cystoscope Makers, Inc*

and nine In the meatal stricture no anesthesia was required and the injection was done directly without the aid of urethroscopy, a 2 cc syringe and a 22 gauge needle being used

Strictures of the anterior and posterior urethra were located and visualized through the Mc Carthy foroblique panendoscope and injection was done with an especially devised endoscopic needle (fig 1) passed through the panendoscope and inserted into the tunica propria beneath the stricture under direct vision The most important feature of this insertion is to get the needle well under the mucosa and into the tunica propria underlying the stricture before the hydrocortisone is injected The injection was done under local intraurethral anesthesia with 1 500 nupercainal solution or, more desirably, under low spinal or general anesthesia as the case indicated With each treatment the stricture was first dilated to its limit of distensibility without rupture Total dosages of 25 mg to 150 mg of hydrocortisone in from one to eight injections were administered When more than one injection was utilized, the successive ones were done in most instances at intervals of 2 days Total dosage and interval of injections were varied at times to suit individual case situations All patients received prophylactic chemo- or antibiotic therapy However, no complications have resulted from the omission of this therapy in our more recent cases with meatal strictures

RESULTS

In fifty-one of the 56 strictures of the urethra or meatus included in this study the results were considered to be excellent with no further clinical evidence of stricture Further dilatations have not been necessary during the current follow up period After having successfully treated 51 cases of stricture the impression remains that the most striking observation is the softness and distensibility of the stricture after the first injection This is of course contingent upon the hydrocortisone being injected into the correct anatomical location

Five of the 56 strictures were found to be resistant to this type of therapy These included 3 cases with multiple strictures and 2 cases with dense elongated strictures of the urethra Reasons for these failures will be discussed below

The following are representative case histories of patients in whom treatment was successful

Case 10 The history of this patient is presented again because this man's

25 years ago This patient had received monthly dilatations in the outpatient department for 5 years with filiforms and followers and never went beyond 16F At the beginning of treatment the urethra was dilated so that a 20F panendoscope could be passed The previously described stricture was visualized and was injected at two sites with a total of 25 mg of hydrocortisone suspension Two days later a 20F rubber catheter was easily passed through the urethra with no preliminary dilatation and the urethra was calibrated easily to 26F The stricture was once again injected Because of the excellent result achieved even after one injection it was not considered necessary to do further treatments in this patient The urethra continues to calibrate easily to 26F

Case 38 This 31-year-old man was admitted to the hospital for a complete urological study as part of an infertility examination At the time of cystoscopy it was noted that the urethral meatus was extremely tight and barely admitted a 20F sound, it was therefore injected with 50 mg of hydrocortisone solution Two days later the urethra was easily calibrated to 30F and has maintained this caliber with no further dilatations or injections

Case 39 This 64-year-old man had a meatal stricture caused by a transurethral resection It was calibrated with difficulty to 16F This was definitely an indurated, stenosed meatus which would have required meatotomy An initial dose of 25 mg of hydrocortisone was injected into the stricture at two sites Two days later the urethra was easily calibrated to 26F and the injection was repeated Five days later the urethra was easily calibrated to 30F and no further treatments or dilatations have been necessary

Case 45 This is the case of a 60-year-old man with a stricture of the membranoprostatic junction due to gonorrhea and of 45 years' duration The stricture previously required at least monthly dilatations and could never be dilated above 22F On admission to the hospital the caliber of the urethra was 16F and a No 20 French panendoscope was passed to the site of stricture The stricture was visualized at the membranoprostatic junction and injected with 25 mg of hydrocortisone at two sites Two days following the initial injection the patient was once again examined and a 24F catheter passed easily through the urethra The urethra was calibrated to 26F with ease and the site of stricture again injected This procedure was once again repeated 2 days later and the patient returned to his home in another part of the country One month postoperatively the patient was examined and the urethra calibrated easily to 26F Since then the patient has required no further dilatations and has had striking relief of his symptoms for the first time in 45 years

Case 30 This 37-year-old male school teacher was seen in consultation because of urethral strictures of 10 years' duration as a result of gonorrhea, necessitating monthly dilatations A urethrogram revealed filiform strictures at the junction of the proximal and middle third of the anterior urethra, and at the neck of the bladder A total of 75 mg hydrocortisone suspension was injected into each of these strictures directly through the panendoscope in three separate sittings After the initial injection, the anterior stricture was markedly softened and the caliber of the urethra was 28F The bladder neck contracture was tighter, but also could be calibrated to 28F Three months later there was no evidence of a filiform stricture which was dilated with a filiform and followers to No. 20F. A No. 20 panendoscope was inserted and the site of stricture was easily identified. The lesion was injected at two sites with a total of 25.0 mg of hydrocortisone suspension. Two days later a 20F catheter passed easily through the urethra with no preliminary dilatation, as did a 24F panendoscope. No clinical evidence of stricture formation could be noted by the passage of the instrument. Inspection of the urethra revealed that the endoscopic picture of the previously noted stricture had undergone change and the bar formation characteristic of it had begun to diminish. This lesion was again injected at two sites with 12.5 mg of hydrocortisone suspension into each. Four days later the caliber of the urethra was 28F. Inspection of the site of stricture with the panendoscope revealed complete disappearance of the characteristic fibrous bar formation at the site of stricture. No injection was done because of the easy distensibility and softness of the previous area of stricture. This patient required no further dilatations of the urethra and to date there has been no further evidence of stricture.

Case 29. A 63-year-old man was admitted for treatment of a stricture of the membranoprostatic junction of the urethra of 12 years duration. This stricture had developed following an episode of urethritis and the patient had been seen sporadically in the outpatient department of the genitourinary clinic. He had required regular dilatations at these visits but his chief complaints were always frequency of urination during the day and marked nocturia. In addition he had a weak, hesitant and intermittent stream. A urethrogram revealed a stricture at the membranoprostatic junction. The caliber of the urethra was 24F. The stricture was seen through the panendoscope and injected at two sites with 12.5 mg hydrocortisone into each. Two days later the urethra was calibrated easily by a 28F sound and the injection repeated. This patient was subsequently followed in the outpatient department and there has been no further evidence of stricture. The relief after this treatment was striking and for the first time in 6 years the patient had no nocturia and no daytime frequency, his stream was strong without hesitancy or interruption.

Case 33. A 77-year-old man was admitted to the hospital for treatment of a filiform stricture of the membranoprostatic junction that resulted from a suprapubic prostatectomy in 1946 and a transurethral resection in 1951. A filiform was inserted through the urethra into the bladder after an extremely difficult manipulation involving 20 minutes and 6 different filiforms. The urethra was then dilated to its limit of distensibility without rupture and a 20F panendoscope inserted. The stricture was visualized and injected at two sites with hydrocortisone solution. Two days after the initial injection a 16F catheter passed easily through the urethra with no preliminary dilatation. The urethra at this time was easily calibrated by a 28F sound. The hydrocortisone injection was repeated and 2 days later, under local anesthesia, the urethra was again easily calibrated by a 28F sound. An injection of hydrocortisone was again given. The patient required no further dilatations and to date has maintained a urethra of adequate caliber.

Case 35. A 71-year-old man was admitted for the treatment of a stricture of the membranoprostatic junction resulting from a traumatic cystolitholapaxy

TABLE 4

	Age of Patient						
	11–20	21–30	31–40	41–50	51–60	61–70	71–80+
Number of patients	1	2	4	5	6	16	17

	Duration of Stricture (Years)						
	New	Newly discovered	1–10	11–20	21–30	31–40	41–50
Number of patients	22	5	15	5	2	0	2

Summary of information concerning age of patients and duration of strictures Note that majority of patients are more than 60 years of age and that few patients are of the younger age group in which strictures gonorrheal in origin, were formerly seen Almost half of the strictures were new or newly discovered, and the majority of those remaining were of two to ten years' duration

TABLE 5

Site of stricture

Meatus	18	Membrano prostatic junction	17
Anterior urethra	12	Posterior urethra	4

Cause of stricture

Unknown	3	Prostatectomy	
Gonorrhea	13	Transurethral	21
Other inflammatory	3	Suprapubic	3
Traumatic	6	Perineal	2

Summary of location and cause of strictures Note relative infrequency of posterior urethral strictures Most common cause was transurethral prostatic resection, the second most common was gonorrhea

Most strictures occurred in the meatus or membranoprostatic junction The posterior urethra was the least common site Transurethral resection of the prostate gland was the most common cause and was found to be so almost twice as often as gonorrhea (table 5)

All but four of the long lasting strictures regardless of their age required dilatations at 4 week intervals or more frequently The patient who had had a stricture for 50 years had needed monthly dilatations (fig 2)

Twenty-eight strictures were filiform in caliber before therapy and seventeen more were 16F or less In one instance the stricture calibrated to 24F but the patient had marked symptoms of urgency, nocturia plus hesitation and interruption of the urinary stream All of these symptoms disappeared following therapy Following treatment all 51 strictures calibrated above 24F (table 6)

The patients who had thirty-three of the 51 strictures have been followed longer than one year and have required no further instrumentation All have been followed longer than their previously required interval of dilatation (table 7) the anterior stricture However, the bladder neck had again contracted This time suprapubic cystotomy was done The bladder neck was markedly contracted and fibrosed A wedge resection of the bladder neck was accomplished and hydrocortisone injected into the cut edges Eleven months following this latter procedure, there has been no recurrence of contracture, and the urethra and bladder neck calibrate easily to 26F

DISCUSSION

The 53 cases of strictures which were observed during the past 2 years have come mainly from three sources as shown in table 2 Initially most strictures were found among hospital outpatient patients but since the appearance of the preliminary paper many recently treated strictures were seen in private practice

The majority of all strictures were cured by three or fewer injections Only two strictures required more (5 and 8 respectively) and this was probably due to the fact that the medication was not injected into the proper location This in part also explains why more than 75 mg of hydrocortisone were sometimes used in an effort to insure proper placement of an adequate amount of the material (table 3)

Thirty-three of the 53 patients were beyond the sixth decade of life This, coupled with the fact that 22 of these strictures were new, confirms the belief that traumatic and postoperative strictures are now more common than the infectious variety (table 4) Four strictures had lasted longer than 20 years

TABLE 2 *Source of patients with strictures*

	Cases
Massachusetts Memorial Hospital (G U Clinic)	14
Beth Israel Hospital (G U Clinic)	16
Private Practices	23
Total	53

TABLE 3

	Number of Injections							
	1	2	3	4	5	6	7	8
Number of patients	6	21	22	0	1	0	0	1

	Total Dosage (mg)									
	25	37½	50	75	87½	100	112½	125	137½	150
Number of patients	5	3	19	14	1	3	1	2	2	1

Number of injections made to cure strictures and total amount of hydrocortisone injected Note that majority of patients required two or three injections, 6 patients were cured by one, and two required five and eight injections respectively Typical total dosage was 50 or 75 mg hydrocortisone Larger amounts were used when *there was some question as to correct placement of material*

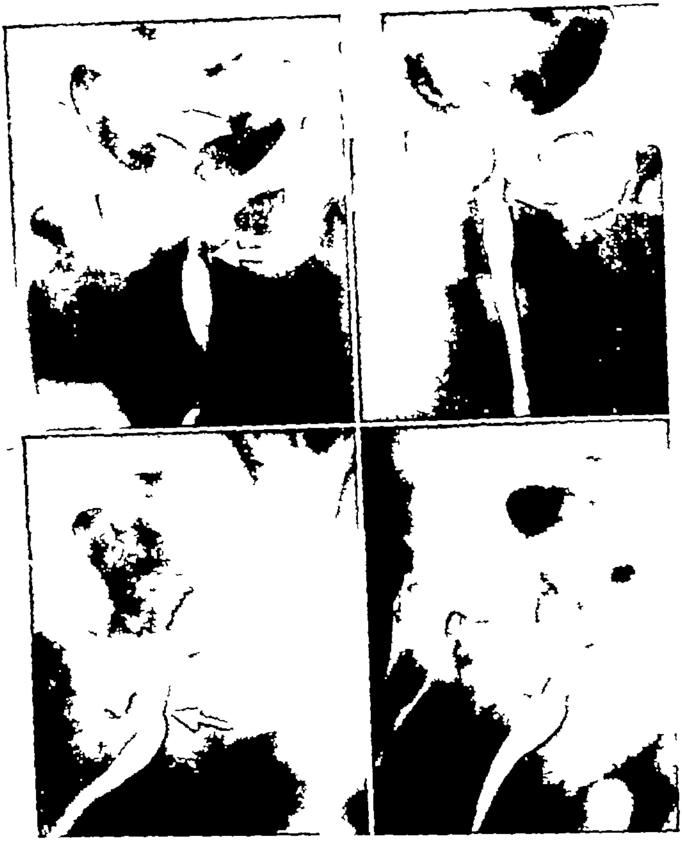


FIG 3 Urethrogram of successfully treated case Above anterior posterior view and below oblique view on left are pretreatment pictures Note definite change in caliber in post-treatment films

of the stricture This represents an actual change and not a distension produced by pressure

Failures were encountered in cases of elongated dense and or multiple strictures which could not be injected throughout their entire length However, even these were not hopeless as they were eventually cured by internal urethrotomy followed by injection of the line of incision with hydrocortisone (table 8 and figure 6)

The success of the treatment depends chiefly upon the technique of the injections The needle must be inserted well into the tunica propria of the urethra, for it is here where fibroblasts are laid down and it is here that fibrolytic action is effective

It is of utmost importance not to overdistend or rupture the stricture by too vigorous a dilatation This only causes increased fibrosis and further constriction. It is sufficient to *calibrate* a urethra to 22 or 24F for most purposes In the absence of symptoms the facile passage of even an 18 or 20F rubber catheter is

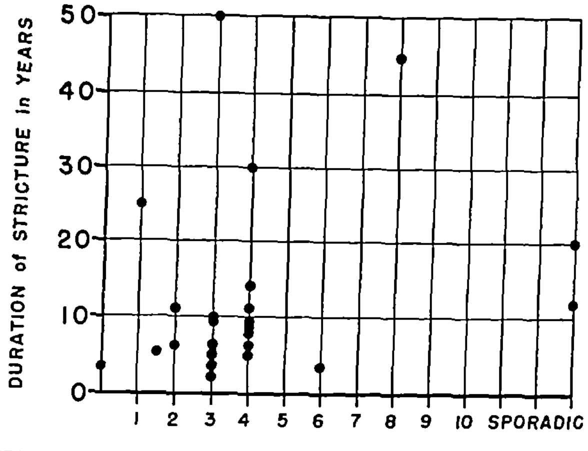


FIG 2 Frequency of dilatations before treatment compared with duration of stricture in all instances of more than 1 year's duration Note that all but 4 cases required dilatation every 4 weeks or at more frequent intervals

TABLE 6

Caliber of stricture before treatment

	Filiform	10-16 Fr	18-22 Fr	24-30 Fr
Number of cases	28	17	5	1

Caliber of stricture after Rx

Number of cases	0	0	0	51

Note that caliber of majority of strictures was below 16F before treatment and that all were above 24F following treatment

TABLE 7 *Duration of followup (months)*

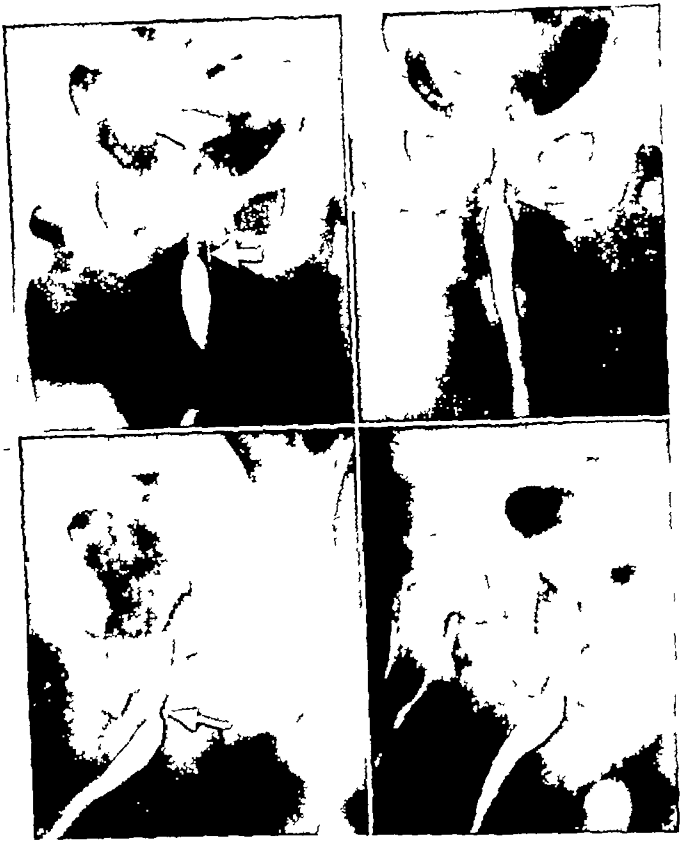
	2-6	7-12	13-18	19-24	25-30
Number of cases	9	9	15	11*	7

* 1 deceased at 15 months

Eighteen patients have been followed more than 18 months and 33 patients more than 12 months In all instances followup period is longer than previous interval of dilatation

Therefore, the treatment just described is effective for the cure of well circumscribed, well defined meatal and urethral strictures It is technically simple, inexpensive, and requires little time It abolishes the chronicity of the disease and does away with the need for life-long therapy

Results have been measurable not only by disappearance of symptomatology and actual urethral calibration, but also by urethrograms Figures 3, 4 and 5 illustrate anterior-posterior and oblique views of urethrograms taken in 3 cases In each instance there is an apparent and visible increase in the diameter



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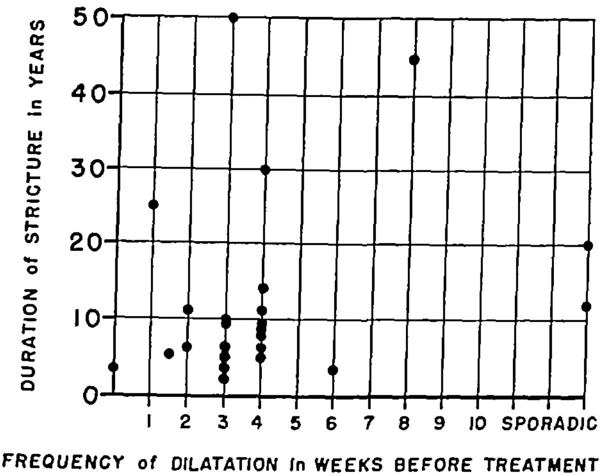

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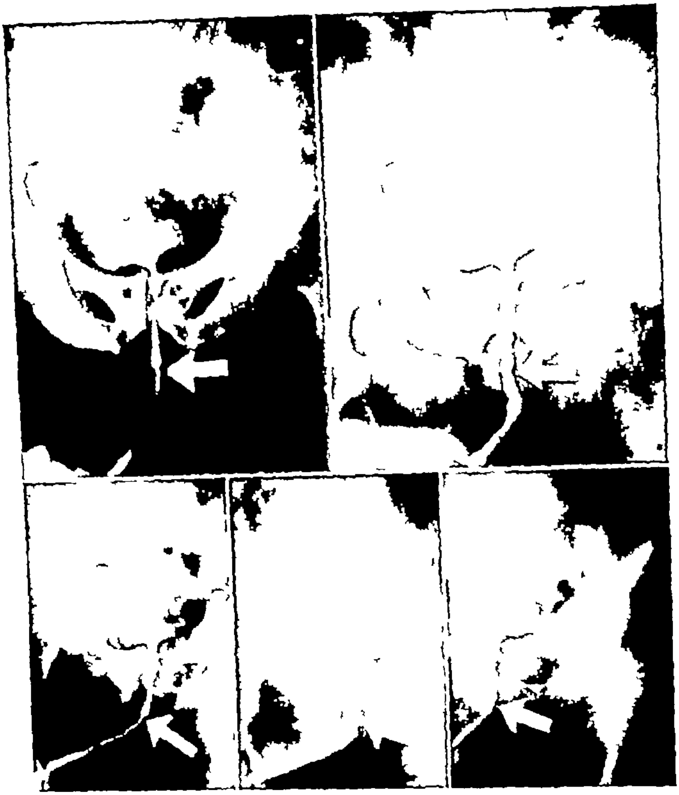


FIG 5 Urethrogram of another successfully treated case Pretreatment films are on left Oblique view shows post treatment films taken at a 3 month interval with corresponding anterior posterior picture, and after 1 year Note definite increase in caliber

there is a fibrolytic effect as well as an inhibitory effect from the injections of hydrocortisone into the area of stricture

The implications of this form of treatment in the field of genitourinary surgery are far reaching It is not only useful in the treatment of strictures of the urethra and meatus, it is now being used prophylactically at the time of transurethral surgery to prevent meatal strictures

With vesical neck contractures there has been variable success Where there has been not too thick a fibrous layer, the results have been good Preliminary observations indicate that the procedure of choice in dealing with a contracted vesical neck is transurethral resection followed by circumferential injection of the area with hydrocortisone

The application of this therapy is recommended as an adjunct in the treatment of vesical neck contractures, pyeloplasty, hypospadias repair, urethroplasty and to all surgical procedures involving the urethra where there might be post-operative stricture formation

Hydrocortisone injected directly into the fresh suture lines of these procedures does not delay healing

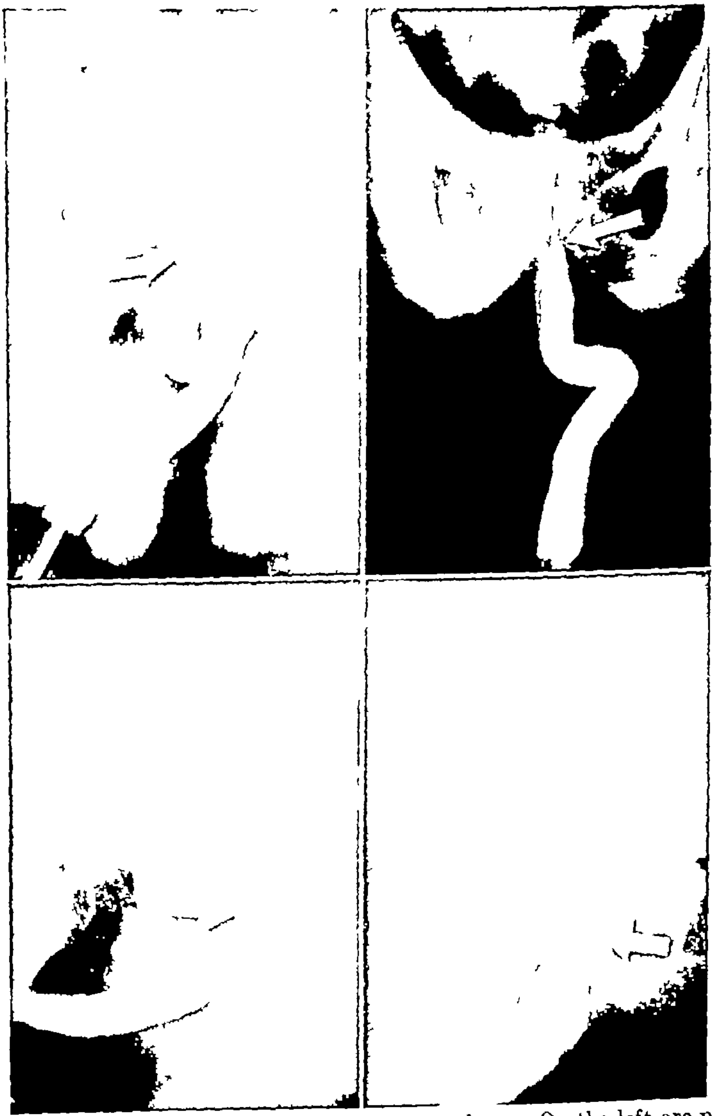
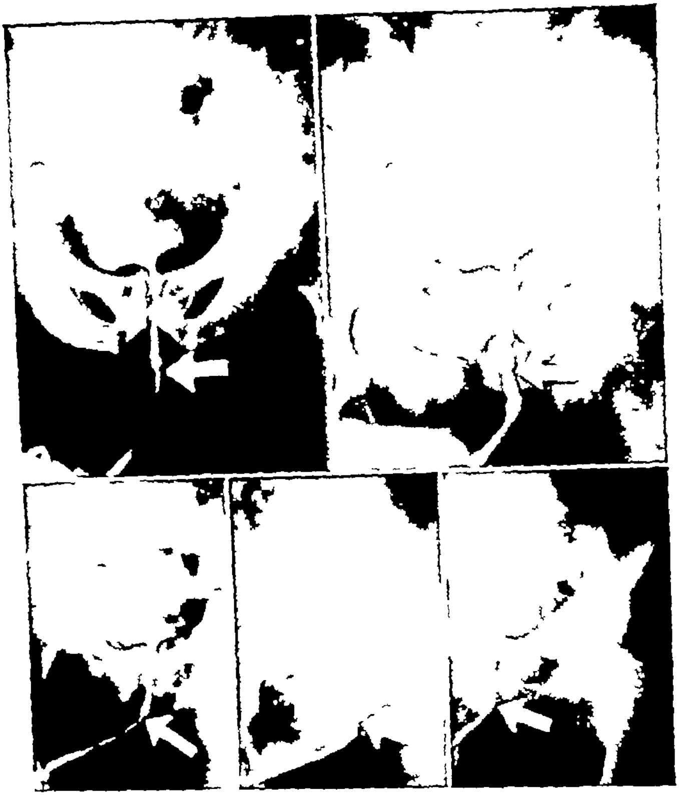


FIG 4 Urethrogram of another successfully treated case On the left are pretreatment films with anterior-posterior view above and oblique view below Note complete obstruction In post treatment films caliber of stricture can be seen to be increased and contrast medium can be seen beyond stricture site

frequently sufficient evidence of an adequate urethral caliber The wanton passage of large sounds may in itself result in the formation of strictures

The success of the treatment bears no relationship to the age of the stricture and bears little relation to the number of injections or to the amount of hydrocortisone solution used We have found it advisable to use the preparation which has 25 mg /cc in preference to those containing 50 mg /cc

It is obviously difficult to prove the disappearance of the stricture histologically We can only postulate at this time, from the evidence at hand, that



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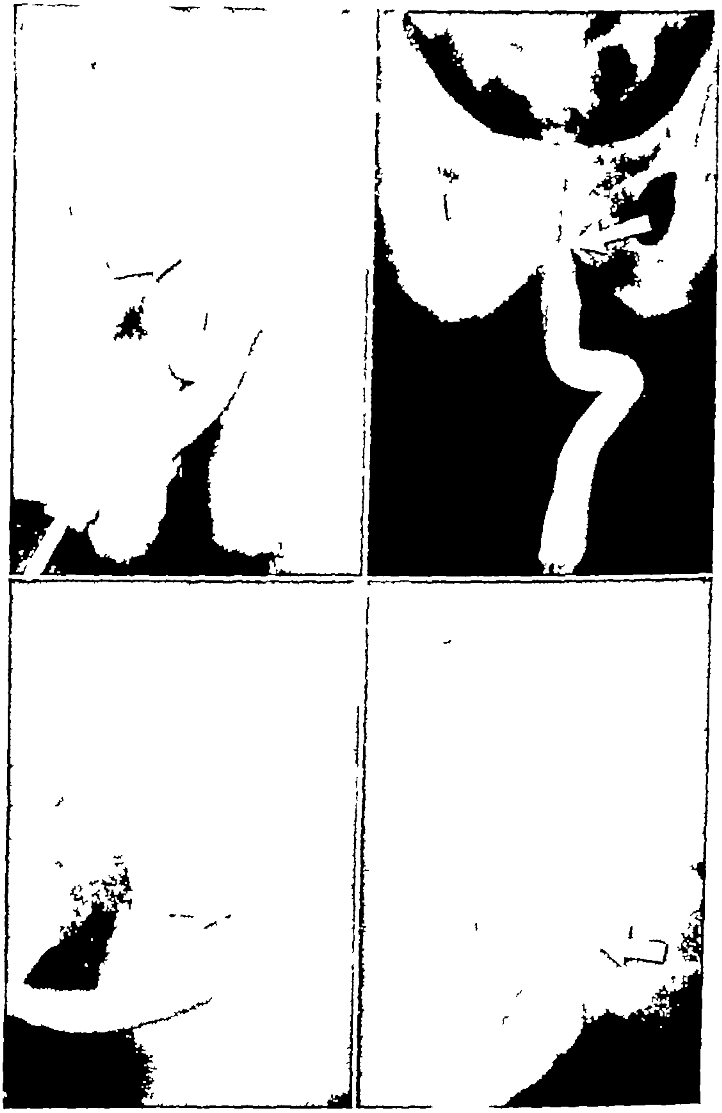

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It is obviously difficult to prove the disappearance of the stricture histologically We can only postulate at this time, from the evidence at hand, that

The direct injection of hydrocortisone achieves results not obtainable with oral therapy and causes no systemic reactions

SUMMARY

Fifty-one well defined, circumscribed urethral and meatal strictures were cured by the local injection of hydrocortisone into the tunica propria below two clock positions of the urethral stricture

Cure was usually obtained with three or fewer injections

Two dense elongated strictures and three cases of multiple strictures not amenable to this therapy were eventually cured by internal urethrotomy and injection of the incision site with hydrocortisone

The authors are grateful to Dr Samuel N Vose, chief of urology, Massachusetts Memorial Hospitals and to Dr George C Prather, chief of urology, Beth Israel Hospital for their advice, encouragement and constructive criticisms

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TABLE 8 *Unsuccessful results*

Pt	Age	Cause of Stricture	Site of Stricture	Cause of Failure
1	70	Traumatic	Posterior urethra	Dense elongated stricture
2	75	Traumatic	Membranous & posterior urethra	Multiple strictures
3	36	Congenital & traumatic	Anterior urethra	Multiple strictures
4	56	Inflammatory	Anterior urethra	Multiple strictures
5	45	Gonorrhea	Anterior urethra	Dense elongated stricture

Strictures in these 5 cases were subsequently cured by internal urethrotomy and injection of hydrocortisone into line of incision

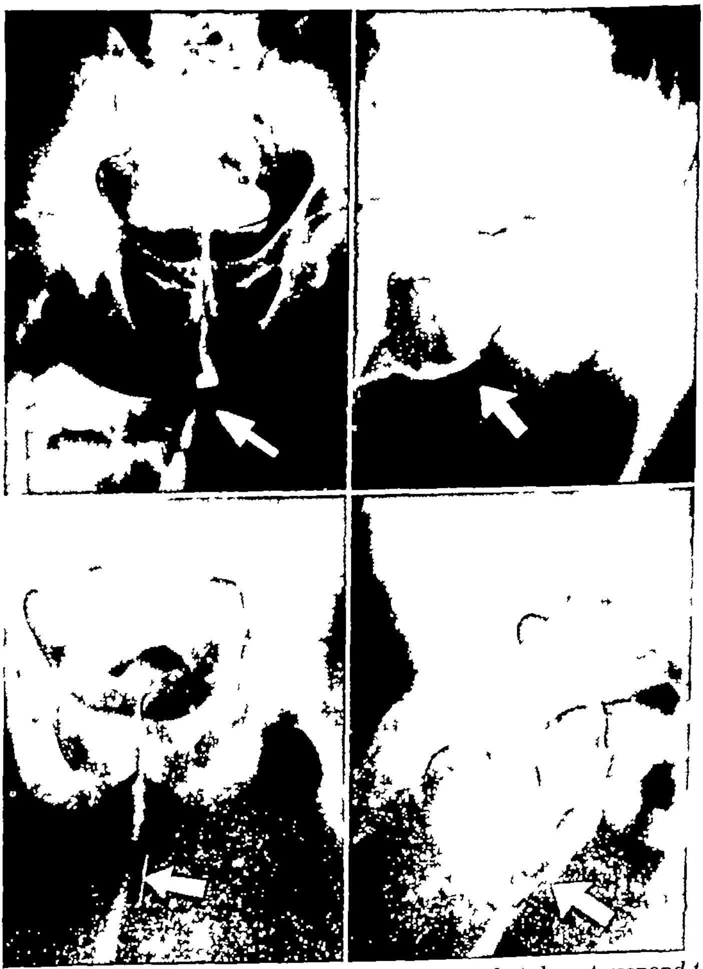

Fig 6 Urethrogram demonstrating types of strictures that do not respond to this therapy Above, anterior posterior and oblique view of urethra with multiple strictures—so called washboard variety Below, dense, elongated stricture is shown in same two views These two types will respond to internal urethrotomy and injection of incision line with hydrocortisone

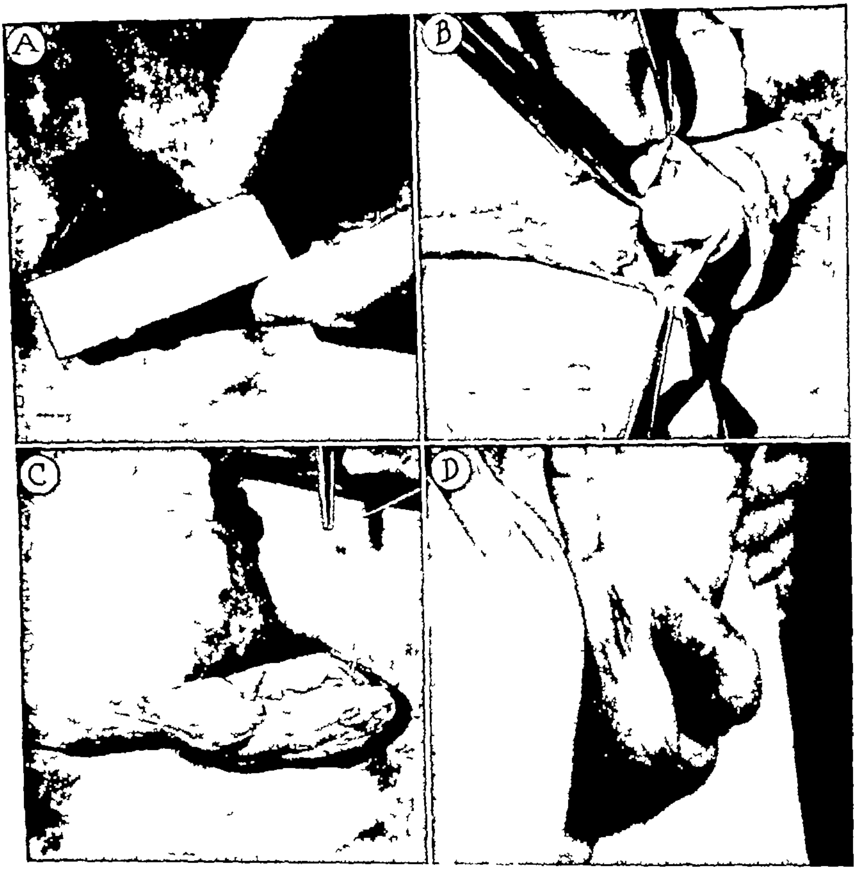

FIG 1 *A*, size of gelfoam before it is rolled into cylinder *B*, cylindrical roll of gelfoam placed within cavity of tunica albuginea *C*, tunica albuginea is sewed loosely with triple O chromic over gelfoam pad, followed by similar suture in tunica vaginalis thus completing new "testicle" *D*, 10 months after operation in which gelfoam was used Note normal contour of scrotum

fascia and skin are then each sewed in separate layers, also with triple 0 chromic over a small rubber drain

The standard commercial piece of gelfoam already packaged in sizes of ¾ by 2¼ by ¼ inches, and used in the first patients, proved to be a little too minute for a good result, except where the testicle was very small A better sized and longer lasting testicle was obtained with a piece of gelfoam measuring 1 by 2½ by ¼ inches, as described

The new "testicle" may look small following this operation (fig 1, c) However, the gelfoam apparently fills with serum and some blood and swells, usually twenty-four hours following the operation The new "testicle" then appears normal in size and shape

By means of this technique the epididymis remains, and the patient can acquire epididymitis as well as anyone else Therefore, it is believed wise to

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TESTICULAR PROSTHESIS FOR AN INTRACAPSULAR ORCHIECTOMY

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The value of orchiectomy in cancer of the prostate is a well established therapeutic procedure There are several methods of accomplishing this result three surgical techniques and two non-surgical

First is the simple classical orchiectomy wherein the entire testicle and epididymis are removed by simply clamping and transecting the entire spermatic cord There is the method of resecting the entire testicle from the epididymis leaving the cord attached to the epididymis, which serves as a small residual "testicle " There is also the intra- or subcapsular orchiectomy, wherein the tunica albuginea is incised and the seminiferous tubules are thoroughly scraped or peeled out from within the capsule of the testis The capsule then is resutured and this also leaves a small residual "testicle" consisting of the epididymis and the empty sutured tunica albuginea A non-surgical orchiectomy can be accomplished by producing atrophy of the testicles by use of x-ray therapy or by large doses of estrogens These latter two methods do not, of course, produce as complete a removal of androgenic producing tissues as the surgical methods

There is no doubt in my mind but that the knowledge of a complete removal of both testicles leaves the patient with a definite psychic upset, consisting of both a sense of physical inferiority and a definite mental depression This, I believe, is in addition to the definite physiological syndrome produced by the sudden removal of androgens It is to counteract this mental reaction that the following procedure of replacing the removed scrotal contents is recommended

TECHNIQUE

See figure 1 The scrotum is opened directly over the testicle The skin of the scrotum is stretched over the testicle by firmly holding the testicle with thumb and forefinger The tunica vaginalis and the tunica albuginea are then incised Still firmly holding and compressing the testicle without changing the original grip the seminiferous tubules are then easily scraped or peeled out of the sac by using the spreading action of a pair of blunt scissors or the handle end of a scalpel This is so far an avascular operation Bleeding is encountered at the base of the tunica albuginea where the blood supply enters the seminiferous tubules This is ligated with a triple 0 chromic suture on a needle A piece of gelfoam, 1 by 2½ by ¼ inches in size, is now lightly compressed and rolled into the form of a loose cylinder (fig 1, *B*) This is placed longitudinally into the sac of the tunica albuginea, which is then sewed loosely with a running suture of triple 0 chromic catgut The tunica vaginalis is also sewed loosely for better drainage The scrotal

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Read at meeting, North Central Section of American Urological Association, Cleveland, Ohio, October 3-5, 1956

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THE SEX CHROMATIN TEST IN CLINICAL PRACTICE

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The urologist may be called upon to determine the sex of a patient or may, at the operating table, be confronted by the need of such information in an apparently normal individual.

Dr. Murray L. Barr and his associates first identified in somatic cells cytologic sex differences. Any such cells of the human body could be used, but those in the skin and from the oral and reproductive tract mucosa have been employed extensively. In females, the resting nuclei contain a special plano-convex chromatin mass usually located at the inner surface of the nuclear membrane. In males, only a few cells may have a similar mass.

Fortunately, we have had the opportunity to send oral smears to the laboratory of Dr. W. O. Nelson. Two ordinary glass slides used in microscopy are employed. Each inner surface of the cheek is gently scraped with a slide and the material spread out. The slides are then immersed immediately while wet into a modified Davidson's solution proposed by Barr. The solution consists of:

Formalin	20 parts
Glacial acetic acid	10 parts
95 per cent alcohol	30 parts
Distilled water	30 parts

Slides remain in the freshly prepared solution usually for 24 hours and then are stained with a modified Feulgen technique and counterstained with dilute light green. The incidence of sex chromatin in a total of 100 nuclei from each smear is determined under oil immersion.

This easy method for sex determination reserves gonadal biopsies and major surgical explorations for confirmation and corrective measures *after* careful study of the patient. In the newborn, when sex is in doubt, a quick decision becomes paramount for a rational plan of treatment. The differentiation of adrenal hyperplasia from some error of sexual development is especially significant in newborn infants. Many of these patients with adrenal hyperplasia do not retain salt and may develop addisonian crises. Cortisone therapy effectively reduces the elevated 17-ketosteroids and dramatic clinical improvement ensues. In both instances, needless surgery is eliminated, future parent-patient anguish and confusion are avoided and future needs of the patient anticipated.

We have seen patients with undescended testes who later turn out to be girls, and recently a girl with a congenital inguinal hernia who was found to have a testis in the sac. These are embarrassing facts to discover at the operating table. A high level of clinical suspicion and use of the sex chromatin test will forewarn and prepare surgeons for these eventualities and, above all, help plan the therapy by foresight.

Read at annual meeting, North Central Section of American Urological Association, Cleveland, Ohio, October 3–5, 1956.

simply ligate or transect the vas deferens at the same time and through the same incision

RESULTS

Fifteen patients have been subjected to this procedure The results have been observed for 1 year In one patient, an 80-year-old man who had only one testicle, a too large piece of gelfoam was used and a subsequent scrotal abscess followed This was corrected by simply ligating and transecting the cord and removing the entire mass of epididymis and "new" testis Since this first case, and since the use of smaller pieces of gelfoam as described, all other cases have healed uneventfully, and the patients have two normal appearing "testicles" The scrotum is usually tender for the first three to five postoperative days, and is relieved by hot packs or hot baths and a scrotal support, which is worn for at least two weeks postoperatively The patient is kept in bed for at least two days following the operation with the scrotum elevated

In the first 3 patients in whom the small pieces, ¾ by 2¼ inches, were used, the gelfoam lasted approximately six months and was apparently almost all absorbed in the course of a year In several others the "testicle" had shrunken to about one-half the original size in the course of a year In the last few cases in which the 1 by 2½ by ¼ inches piece of gelfoam was used, the size appeared almost normal with very little absorption at the end of 10 months The patient does not complain of the gradual atrophy as much as the sudden absence of both testicles that follows a complete, routine orchiectomy

30 S County Line Rd , Hinsdale, Ill

W H , a 33-year-old white "man," complained of infertility of several years' duration On physical examination the beard and axillary hair were absent The breasts were enlarged, the pubic hair of female distribution The penis and scrotum were normal and both testes were small A semen sample contained no spermatozoa, the gonadotrophins were at castrate levels Bilateral testicular biopsies showed tubular sclerosis and adematous masses of interstitial cells An oral smear revealed cells of the female type A diagnosis of Klinefelter syndrome was made

R J , a 17-year-old white girl, had a genital deformity investigated at the age of 5, laparotomy showed a uterus and tube on the right and some structures suggesting gonads, the histology of which was indeterminate The vagina and cervix were visualized by endoscopy At age 14 cyclic estrogen therapy was begun and at present, menses are regular with estrogenic withdrawal An oral smear showed cells of the male type Urinary gonadotrophins rose to castrate level when estrogen was withheld for one month Most likely diagnostic classification is Turner's syndrome (gonadal dysgenesis)

Three of these 5 cases seen in the past year had had unnecessary surgery to establish sex The easily used chromatin test would have reserved surgery for plastic procedures where indicated The psychiatric, anatomical and social factors can be evaluated before operation and a course of therapy envisioned

The urologist must be alert and suspect some error of sexual development in patients with undescended testes, small scrotal gonads, lack of beard, gynecomastia, enlarged phallus, congenital hernia and amenorrhea His suspicion can easily be confirmed by the simple chromatin test

A 10-year-old-boy was referred by Dr Frederick Brush of Mason City, Iowa The mother thought the boy's genitalia were smaller than normal Physical examination revealed slight obesity and normal appearing genitalia The oral smear was reported sex chromatin positive (female type) Bilateral testicular biopsies revealed that many tubules were devoid of germ cells, some contained gonia and others, oocytes Since the only known instances of positive chromatin test in "males" have been in Klinefelter's syndrome it is our impression that this case, a sex chromatin-positive prepubertal boy, will develop this syndrome (Case presentation at the annual meeting of the Clinical Society of Genito-Urinary Surgeons, Iowa City, Iowa, February 7 and 8, 1957)

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Girls with dwarfism, infantilism, webbed neck and coarctation of the aorta (Turner's syndrome) show, in the majority of cases, male type somatic nuclei An early diagnosis of gonadal dysgenesis can be established and the necessary estrogen prescribed at puberty

In Klinefelter's syndrome seen in infertile males, the sex chromatin test will be of the female type and a ready differentiation from other types of "testicular" atrophy can be made

CASE REPORTS

K H , a 4-year old "boy," one of twins, was seen for advice about undescended testes During the past 6 months prior to consultation, the patient had grown rapidly, facial pimples appeared and vocal tones were low On examination the patient was large for his age He had mild facial acne The pubic hair was coarse, marked chordee of the phallus was present with the urinary meatus at the penoscrotal area Testes were not palpable in a well developed scrotum An oral smear revealed cells of the female type and the urinary 17-ketosteroids were elevated The resident staff, unconvinced by the oral smear information, performed an urethrogram which showed a normal posterior urethra confirmed by endoscopy At operation two ovaries and tubes, and a uterus were found The 17-ketosteroid excretion quickly dropped to normal levels following cortisone therapy A diagnosis of female pseudohermaphroditism with adrenal hyperplasia was made in a patient with "undescended testes " Delay in the diagnosis of sex has raised the question whether this girl should be reared as a boy It is no easy matter for parents who bring in their boy, especially a twin, for undescended testes and find out "he" is a girl No corrective surgery was performed at the initial exploration, but the internal sex organs were later removed surgically and a plan of therapy was initiated toward the establishment of male genitalia

In contrast to the preceding case, D T , a premature Negro infant, had genitalia suggesting undescended testes and hypospadias in a male or an enlarged clitoris in a female The oral smear was of the female type and the 17-ketosteroids were markedly elevated Cortisone therapy greatly reduced the latter and the child gained weight Quick recognition of the true sex and adrenal hyperplasia resulted in a planned management The biological hardships of prematurity are severe enough without complications such as these Further, this girl will never be considered a boy with undescended testes

K S , an 11-year-old white "girl," had noticed a gradually increasing, painless right inguinal mass for 3 years Examination showed a reducible, non-tender, soft inguinal mass above the labium At surgery a testis (later histologically proven) was found and a biopsy taken Pelvic examination showed a normal clitoris, labia and vagina No cervix could be found The sex chromatin test revealed cells of the male type A diagnosis of male pseudohermaphroditism was made This case suggests the advisability of routine use of the sex chromatin test in all cases of inguinal hernia in girls This patient has two siblings with suspected hernias and the chromatin tests will be done before their herniae are approached surgically maturation of the germ cell the number of chromosomes is reduced from 48 to 24 one of each pair going to each daughter cell Thus, although all mature ova contain 23 somatic chromosomes plus an X chromosome, half of the spermatozoa contain an X chromosome and the others a Y chromosome Fertilization of an ovum by a spermatozoon bearing an X chromosome then results in the development of a female, while fertilization by a Y bearing sperm results in a male Actually it has been demonstrated in insects that the Y chromosome has no sexual influence for an individual developing with only one X chromosome is a male whether or not there is a Y chromosome

However, sex in the early embryo is only potential, since the gonad is an undifferentiated cell mass along the urogenital ridge until the sixth to eighth week In XY individuals the central cells of the gonad proliferate and form testicular tubules, and in XX embryos the cortical portion of the gonad differentiates a few days later into the ovary

Once the gonad is established, the further development of either the wolffian or müllerian structures, with atrophy of the other, apparently depends on the presence or absence of hormones from the interstitial cells of the fetal testis Burns has shown that removal of testes from the pouch young of the opossum results in their development as females Therefore, gonadal dysgenesis (Turner's syndrome) may result from injury to the testis of an XY embryo at the time of gonadal differentiation An individual, morphologically female is then produced by default as it were, of the testicular influence This is strongly suggested by the finding that most of the patients of this type lack the extrachromatin mass characteristic of female nuclei

Maternal as well as other fetal hormones may affect development similarly, since treatment of pregnant rats with hormones will result in litters which are grossly all of one sex It has been noted that the effect of the fetal testis is mainly local, the genital structures in lateral hermaphrodites developing along male lines on the side of the testis and in a female fashion on the side of the ovary Hormones carried in the bloodstream, however, and acting on the genital structures very early in their differentiation may obviously be responsible for various types of pseudohermaphroditism

The later occurrence of endocrine disturbances affect the external genitalia In their undifferentiated state, these consist of the phallus, later to become the penis or clitoris, the labioscrotal swelling and the urogenital folds which close to form the male urethra In the adrenogenital syndrome, androgens from the adrenal cortex are responsible for the large phallus and other changes which constitute pseudohermaphroditism in newborn females It is evident that this is a late effect since the ovaries and the internal genital organs are essentially normal That endocrine disturbances producing intersex children may be on a genetic basis is evident by their familial occurrence in some instances Genetic abnormalities may produce individuals incapable of manufacturing particular hormones, or in whom the tissues are incapable of responding to normal hormonal stimuli

There is also some evidence that there are somatic genes for maleness and

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SEX CHROMATIN DETERMINATION IN INTERSEX STATES

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Until relatively recent, laboratory procedures directed toward the study of intersexuality have been confined to histologic identification of gonads as ovarian or testicular, and to determinations of steroid and gonadotrophic hormone levels These methods have helped to clarify the status of many intersex patients

However, the work of Dr Murray L Barr, of the University of Western Ontario, in developing methods for determination of the nuclear sex pattern has opened up a wide field for further investigation Doctor Barr discovered that, in females, a mass of chromatin could be identified in the nuclei of most cells which was not present in males (Barr 1949, Moore and Barr)

Sex differences in nuclear chromatin have been identified in the human, in some insects, and in most mammals except for certain rodents and the rabbit (Moore and Barr) In the human, the sex chromatin mass is usually less than 1 micron in diameter and is found on the inner surface of the nuclear membrane, having a rounded, planoconvex or angular appearance Theoretically, this chromatin mass appears in all cells of the female although in pyknotic nuclei or those whose chromatin is characteristically heavily clumped, it cannot readily be distinguished The sex chromatin mass can be identified only in intermitotic or resting nuclei, when the chromatin is generally in a finely granular or fibrillar state, and is thought to represent the mass of the two paired X chromosomes With the Feulgen and methyl green-pyronine stains, it, like the remainder of the chromatin, is found to consist of desoxyribose rather than ribose nucleic acid

Barr (1955, a) and others (Hunter and Lennox, Sohval and Gaines, Tavaras) have found that tumors retain the sex chromatin characteristics of the host, except for some testicular teratomas which have female type nuclei In pseudohermaphrodites the sex chromatin usually matches the gonadal sex but in Klinefelter's syndrome (testicular hypoplasia) the cells are usually chromatin-positive or female It was surprising also to find chromatin-negative or male type nuclei in most cases of Turner's syndrome (ovarian or gonadal dysgenesis) The cells of true hermaphrodites may contain positive or negative nuclei (Barr, Bradbury, Bunge and Boccabella, Greenblatt, Mateo de Acosta and Vasquez, Grumbach, Engle, Blanc and Barr, Moore, Graham and Barr, Plunkett and Barr, Sohval, Gaines and Gabrilove)

These observations have led to a review and recontemplation of what is known about the heredity and differentiation of sexual characteristics In the normal course of events, the sex of an individual is determined at conception by the chromosomal makeup of the spermatozoon effecting fertilization This is presumably entirely a matter of chance, since in one of the divisions during the

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Read at annual meeting, North Central Section of American Urological Association Cleveland, Ohio, October 4–6, 1956 this type so the *cresyl echt* violet stain is used for smears. Again, 100 cells whose nuclei are in the resting phase are counted and the percentage of those containing the characteristic chromatin mass determined.

The discovery of a difference between the cells of a male and those of a female is in itself an advance of first importance. The working out of a technique by which such a determination can be made by a simple clinical test is even more remarkable.

The clinical implications of Barr's discovery were immediately apparent to himself and to many others who heard of it. It seemed that here at last was a sure way to determine the true sex in persons in whom there was difficulty or doubt in such determination.

Barr immediately applied the method to some cases of hermaphroditism, or as we now prefer to say, of intersex states. At first it seemed to fulfill the initial promise and did prove to be very helpful in many patients. However, as the test was applied more widely, some rather astounding findings were made and continue to be made.

At this point we should go back briefly and see what the situation was before this test was evolved. For many years the criterion of a person's sex was the histological pattern of his gonads. It was known that the pattern of external genitalia and secondary sex characteristics, as well as the hormonal and psychic patterns might deviate from those appropriate to the gonads present. However, there was no realization that there could be a major discrepancy between the basic sex chromatin pattern and the type of gonad which developed. Since there was no way by which the sex chromatin pattern might be determined, the possibility of such a conflict was not entertained by most people, certainly not by urologists.

Since the presence of the XX or the XY chromosome pattern is still, as far as we know, the most basic and fundamental difference governing the development of one sex or the other, the apparent ability to determine this pattern clinically added another major diagnostic factor which it seemed, at first, would supersede all the others. At present, however, it is evident that the sex chromatin pattern is only one of the factors which determines the individual's sex.

It is still not possible to give a simple definition of sex. The definition we have worked out for ourselves is neither brief nor exact, but at the present it is the best we can do. It is stated in terms of the various sex determining factors. These are 1) the chromatin pattern of the individual cells, which in turn is presumably determined by the presence of an X or a Y chromosome in the sperm which fertilizes the ovum 2) the nature of the gonadal structures. This is apparently determined not only by the sex chromosome pattern, but also by other genes which directly govern gonad development as well as possibly by extrinsic factors acting during the developmental period 3) the hormonal pattern, which we find is dependent on the development of the gonads and the other endocrine organs, regulated both by genetic factors and other influences, 4) the genitalia, both external and internal, and the secondary sex characteristics, all of which are influenced by the chromosome pattern, by the hormone pattern, and by separate femaleness affecting all of the tissues of the body, including the genital tract, independent of the gonadal or chromosomal pattern The influence of such genes may override that of the chromosomal pattern of an individual and thus produce a pseudohermaphrodite Human pedigrees have been recorded, a series of which contained 28 normal females, only 8 normal males and 22 intersexes, suggesting strongly that a dominant gene carried by normal females submerged the XY genetic constitution and resulted in a large number of male pseudohermaphrodites

True hermaphroditism may also be related to familial genetic factors, but is thought to be due more often to accidental confusion of chromosomal elements

In the workup of clinical intersex problems, sex chromatin may be demonstrated in any convenient way, the usual method being to search for it in the epidermal nuclei of skin biopsy sections or in squamous epithelial cells removed from the oral mucosa by scraping The technique of obtaining and handling these specimens is critical, since the chromatin mass is very small and optimal conditions of fixation and staining must be maintained in order to properly evaluate the specimen These methods have been described in detail by Moore and Barr The skin biopsy, for instance, which may be taken from the volar surface of the forearm or from the abdominal wall must be fixed immediately in a modified Davidson's solution This consists of two parts of formalin, 3 parts of 95 per cent alcohol, 1 part of glacial acetic acid and 3 parts of distilled water The tissue must be transferred after 24 hours to 70 per cent alcohol for 24–48 hours and then carefully imbedded in paraffin Sections must be cut at 5 micra or less and stained, preferably with Feulgen technique At no time should the tissues or sections be heated more than is absolutely necessary The Feulgen stain is used because of its specific staining of desoxyribose nucleic acid Other nuclear stains, such as hematoxylin, also stain the nucleolus and other ribose nucleic acid structures which may give rise to confusion The squamous epithelial cells in the mid-portion of the epidermis or the prickle cell layer are usually the most suitable for examination One hundred such cells, whose nuclei are in the resting phase, are counted Obvious extrachromatin bodies will be found, usually attached to the inner surface of the nuclear membrane, in 30–80 per cent of the nuclei in normal females Chromatin masses, which may appear similar to these, are found in very few (usually less than 10 per cent) of the nuclei of male tissues

For smears of epithelial cells from the oral mucosa or other moist surfaces, such as the vagina, it is important that the slides be coated with albumin of the type used in mounting histologic sections so that the cells will adhere to the slide Scraping of the mucosal surface should be vigorous so as to obtain cells from the intermediate rather than entirely from the superficial layer Scanty material should be smeared in a small area on the slide since the examination must be performed under oil immersion and widely separated cells cannot be located at this magnification The smears are fixed immediately in Papanicolaou's ether-alcohol solution, consisting of one part ether to one part 95 per cent ethyl alcohol Drying of the cells in air before fixation destroys chromatin detail The Feulgen stain is rather unpredictable and often too pale for specimens of appears in males However, males so afflicted are not intersexes and will not be considered here

The great value of the sex chromatin determination has been in helping to make an early, reasonably certain diagnosis of the condition without surgical exploration Formerly, these patients were subjected to laparotomy for biopsy of the gonads and determination of the presence or absence of the internal female sex organs as well as for the purpose of detecting enlargement of the adrenals

At present, the sex chromatin study will establish the genetic female pattern Hormone studies of the urine will detect the increased amounts of 17-ketosteroids being formed, and this is usually adequate to allow beginning of treatment with cortisone In those cases with congenital hyperplasia, the 17-ketosteroid output falls promptly on administration of the cortisone If it does not tumor is suspected and further studies, such as retroperitoneal air insufflation are done to detect the possible presence of tumor The only surgery now necessary in these adrenogenital cases is clitoridectomy and plastic reconstruction of the vulva to restore the external genitalia to a female pattern

In the case of male pseudohermaphroditism the skin biopsy test will confirm the male pattern usually found in the gonads under these circumstances In true hermaphroditism where the gonads show both male and female histologic characters the sex chromatin pattern may be either male or female Usually, under these circumstances, the character and adaptability of the external genitalia will weigh heavily in the assignment of sex

One of the remarkable things was the finding that in many cases of gonadal dysgenesis (formerly known as ovarian agenesis) the chromatin pattern was not female These individuals show infantile undeveloped female secondary sex characteristics and genitalia as well as some other anomalies such as web neck and coarctation of the aorta There is complete lack of development of the gonads Apparently the female somatic patterns develop by default so to speak or more probably the lack of gonadal development is only part of a deeper and more profound genetic fault Despite the finding of the male sex chromatin pattern, these individuals should be raised as females With hormone treatment the external genitalia and secondary sex characteristics can be caused to develop and these patients can lead a reasonably happy life as females It would be foolish to attempt to convert them into males on the basis of sex chromatin By the definition of sex given earlier, the finding of an XY (or negative) chromatin pattern does not shift these individuals to the male sex

The most recent unexpected finding has been that certain cases of testicular hypoplasia have a sex chromatin-positive pattern This syndrome was first described by Bronstein one of the co-authors of this paper, and later by Klinefelter, Reifenstein and Albright Clinically these individuals present the picture of male hypogonadism with poorly developed genitalia small undeveloped testes, gynecomastia and sometimes eunochoidal characteristics such as obesity poor hair growth and high voice The picture is one of male underdevelopment rather than of feminization Attempts to convert this type of individual to female on the basis of the sex chromatin pattern would certainly be unwise

In conclusion, we may say that the determination of the sex chromatin pattern genetic controlling influences, 5) the last, the psychic pattern This is influenced by the hormonal pattern as well as by the upbringing and education of the individual

No single one of these factors is a reliable guide to determination of sex, and the definition we have finally arrived at is as follows "Sex is the overall state of body and mind by which the individual conforms to the male or female standards of normality in the above named sex determining factors " It is a summation of these factors in which no one supersedes the others There is no single conclusive determining factor Every person is a mixture of male and female characteristics, and it is the sum or preponderance of all these factors which determines sex and not any single one or two of them We shall mention only briefly the clinical methods by which these various factors are determined in the intersex patient, since they are well known to most of you

The sex chromatin pattern can be determined as described above The gonadal pattern can be determined with certainty only by histologic study of a biopsy specimen, and this is done wherever necessary The hormonal patterns can be determined by appropriate chemical tests, usually of the 24 hour urine output The clinical examination of the genitalia includes in many cases cystoscopic study for detection of uterovaginal structures when these are not externally apparent In some cases, laparotomy is necessary to determine the character of the internal genitalia with more accuracy

The other secondary characteristics are usually evident Determination of the psychic pattern or orientation of the individual may be difficult, particularly in children and should be done by psychiatrists who have a special interest in this group Very extensive studies along this line have been done recently and reported by Money and the Hampsons at Baltimore

The final assignment of sex in any given individual is made only after all these factors have been determined as accurately as possible and considered by the physicians concerned It is impossible to assign any fixed table of relative values to the various factors Because of their importance in the adjustment to one sex or the other, the genitalia and secondary sex characteristics, while not of primary biological significance, assume a very important clinical role because they govern the potential adaptability of the individual to one or the other sex The clinician who has to make the necessary correction is always very much influenced by this factor The final sex for the individual will usually be that which fits the gonadal, chromosomal and genital sex patterns best Hormone patterns can often be corrected medically Psychic patterns will usually give little trouble if the proper determination is made early enough in life

We should like to take up now the different groups of intersex patients and show in what way the sex chromatin determination has been important or of value

By far, the largest single group of intersex patients is the adrenogenital group Until recently, only the genital effects were realized Now, it is known that many of these patients also have electrolyte disturbances which require treatment and may be very serious threats to the patients' life, particularly in infants We shall not go into this aspect of the problem at this time This syndrome also

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THE USE OF NEOMYCIN AS A COLD STERILIZING AGENT

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The sterilization of urological instruments has been of great concern to urologists for many years In the last 10 years various agents have been introduced and some have been discarded The most recent agents to come into the field have been the quarternary ammonium compounds These sterilizing agents do a reasonably good job but have two major disadvantages The first disadvantage is that the agent has to be washed off the instrument before its insertion into the urethra and secondly, these sterilizing compounds are also wetting agents and consequently they make our instruments very slippery and easy to drop Oxycyanide of mercury is still widely used chiefly because of its economy and also because it does not make instruments slippery However, it should be observed that the addition of a even midly acid salt to a mercury cyanide solution releases poisonous hydrocyanic gas All in all, these various cold sterilizing agents have certain limitations insofar as their effectiveness against a wide range of bacteria All of us have had the unhappy experience of reading the bacteriology report which says "contaminants" Certainly no cold sterilizing agent is a perfect bacteriocide under all conditions Our instruments, of course, require meticulous care There is no substitute for good cleansing to remove spore formers, following which the instruments should be dried completely

It seems to me that certain properties are necessary for a good cold sterilizing agent First, we want an agent that would be effective against a wide spectrum of bacteria Secondly, we need an agent that would have to be washed off the instrument prior to its insertion into the urethra Thirdly, we want an agent that would not make the instrument slippery And lastly, we want an agent that perhaps under certain conditions would be possible to use over and over and over again This last property I felt would fit in with the economics of the situation We then recalled the work of Roth, Kaminsky, and Hess concerning the use of neomycin in pyelographic media, and we immediately began to consider the use of neomycin as a cold sterilizing agent [1]

Neomycin in solution is effective against a wide spectrum of bacteria, if used it would be an agent that would not make our instruments slippery, and is so non-toxic when applied locally it would not have to be washed off the instrument prior to its insertion into the urethra [2] And, according to the work of the Upjohn laboratories, it has been shown that sterile solutions of neomycin retain their activity at 37°C for at least five months and probably much longer Neomycin develops a yellowish tinge after a while but this in no way implies loss of activity In neutral and acid conditions it is stable at boiling temperatures for more than

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has been very helpful in the management of the adrenogenital group of patients, and useful in male pseudohermaphrodites and true hermaphrodites

In the study of ovarian agenesis, and testicular hypoplasia, the results have been exceedingly interesting from the academic point of view and should be studied further, but at the present time the findings do not warrant any radical change in our mode of treating these patients

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SOME CONSIDERATIONS IN THE ADMINISTRATION OF NOVOBIOCIN AND CYCLOSERINE

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Novobiocin is marketed under the trade names of cathomycin and albamycin and, while derived from different streptomyces, the end-products are identical antibiotics There is a higher blood level than usual with other antibiotics in like dosage due to slower urinary excretion There is consequently a lower urine content but sufficient to produce bacteriostasis of sensitive organisms There is some excretion in the feces which accounts for loose stools in about one-third of the patients and, occasionally, diarrhea

It is obvious that novobiocin is not a broad-spectrum antibiotic since coccal organisms chiefly are sensitive It is unique in that of all the gram-negative bacilli only Proteus is sufficiently sensitive to warrant its use There is considerable variation in the degree of sensitivity of different strains of Proteus Sensitivity of staphylococci appears independent of their resistance to penicillin or erythromycin At present its most likely indications are for urinary infections due to staphylococci known to be resistant to penicillin or erythromycin or the patient is known to be sensitive to these antibiotics

The chief side reaction to novobiocin is of a dermatologic nature, such as rashes and urticaria, which will occur in up to ten per cent of patients when the drug is administered longer than six or seven days These usually clear up within a week after discontinuance of novobiocin The incidence is in proportion to dosage and duration of therapy Welch and his co-workers[1] reported recently that of 208 adult male volunteers who were given 1 gm novobiocin daily for 5 days followed by a rest period of 2 days and then by a second similar course only one patient exhibited a drug rash However, two of three patients given novobiocin on this schedule had rashes after the onset of the second course Hence, at present, a 5-day course only is recommended

When the urinary infection is known to be only coccal in etiology it would seem justified to administer novobiocin alone, especially if there has been a previous failure of cure on penicillin or erythromycin In the presence of mixed infections more observations are needed to determine the best antibacillary agent to combine with novobiocin It is likely that a sulfonamide in half dosage will prove safe and helpful, also infections due to Proteus and Streptococcus faecalis will require additional chemotherapy Increased resistance of bacteria to novobiocin tends to appear during the course of treatment when it is used alone Seven of eight patients with Proteus infections given novobiocin only failed to be cured, although in some patients cultures were negative during its administration

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Read at annual meeting North Central Section of the American Urological Association, Cleveland, Ohio, October 3-5 1956

[1] Welch, Henry Lewis C N Putnam L E and Randall W A A study of sensitizing potential of novobiocin Antibiotic Med Clin Therapy, 3 27-32 1956

an hour Neomycin has been found to be bacteriocidal against Proteus vulgaris, Pseudomonas aeruginosa, Escherichia coli, Aerobacter aerogenes, Micrococcus aureus, Streptococcus faecalis and others Consequently we have in neomycin an agent which meets our criteria for possible use as a cold sterilizing agent Our next step then was to determine what per cent solution of neomycin would be effective

Our initial experiments concerned the use of neomycin in a 1 per cent solution for a 6-month period We allowed our instruments to soak at least 30 minutes using this 1 per cent solution After using this solution over and over again in over 200 routine infected and uninfected cystoscopies for 6 months, we then performed the following experiment May I add here that we did not use neomycin in any case where there was a suspicion of genitourinary tuberculosis We felt that in an experimental procedure it was not fair to subject any patient to the possibility of exposure to this disease

Using this 6 months' old solution of 1 per cent neomycin, we inoculated our cystoscopes with a pure culture of Micrococcus aureus These cystoscopes were then immersed in the solution for periods of 15 minutes, some for 30 minutes, and some for 45 minutes, and cultures were then taken From the observation of these cultures we came to these conclusions 1) Neomycin was still effective against Micrococcus aureus even after 6 months use and 2) we observed that 30 minutes was the ideal sterilizing time for this organism About this time we received a communication from Dr J A Dugger of the Upjohn laboratories indicating that the use of neomycin in a 5 per cent solution was effective in 1 minute against Pseudomonas aeruginosa, Proteus vulgaris, and Micrococcus aureus[3] Consequently, this added another advantage to the use of neomycin as a cold sterilizing agent, that is, rapidity with which it could sterilize our instruments Therefore, we began to use the 5 per cent solution This has constituted the last 6 months of our experiment, a period in which we were able to repeat our findings using, however, a culture of Proteus vulgaris against which a 5 month-old neomycin solution of 5 per cent solution was still bacteriocidal in 10 minutes To this date we have had no case in which there is any evidence of toxicity to a patient We have had no case in which there is any evidence of cross infection from one patient to another And, we have also had the advantage of using instruments that were not slippery, that did not have to be immersed in water after their sterilization, and of which we were most certain that adequate sterilization had been performed

In summary, the use of neomycin as a cold sterilizing agent for urological instruments has been presented, certain preliminary data on its efficacy have been outlined, and other experimental data on its use in our hands are available if desired, but which could not be presented within the time limitation of this paper

Grateful acknowledgment is made to Upjohn Company, Kalamazoo, Michigan, for liberal supplies of mycifradin sulfate (neomycin)

1040 Delaware Ave , Marion, Ohio

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[3] Dugger, J A Personal communication to author, March 28, 1956

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RESULTS OF THERAPY WITH FURADANTIN IN SMALLER DOSAGE

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This is a report of experimental and clinical studies of nitrofurantoin (furadantin) and covers a period of approximately twelve months, June 1955 to June 1956.

It has been noticed in the clinical use of furadantin that a high percentage of acute urinary infections will subside rapidly on the recommended dose of 100 mg. 4 times daily. We have also found that almost as good results can be had on smaller doses. Since some gastric irritation and nausea may occur with a large dose, we have tried to determine when and why a 50 mg. dose will be just as effective in producing sterile urine.

It was at first decided to include only acute nonsurgical infections in this study, but later 61 postoperative surgical patients were added to this report, making a total of 188 patients. Of this total, 73 patients received 50 mg. furadantin 4 times daily. Before starting treatment a urine culture, a gram stain and sensitivity study were made in each case. The tube dilution method was used to determine sensitivity and this may account for a slightly higher rate of resistant organisms in this study than usual. Resistance to furadantin did not influence the size of the dosage used in this series, however, after 1 week if the culture was still positive the result was recorded as a failure and the dose was then increased or the drug changed entirely if this seemed advisable.

Results are presented in these comparative groupings:

1) In vitro sensitivity and its relationship to the size of the dose of furadantin.
2) The relationship of the Gram stain to the size of the dose.
3) Whether the infection is from a single organism, or a number of different organisms.

When the organisms were found to be sensitive in vitro, the percentage of negative cultures after one week's treatment with 50 mg. of furadantin 4 times daily was equal to the percentage receiving 100 mg. doses, whether the organism was gram-positive or gram-negative.

There were 127 cultures with organisms found sensitive to furadantin in vitro (table 1). Seventy-seven patients received 50 mg. doses 4 times daily and of these 73 showed negative cultures in one week. This is a 94 per cent cure rate. Fifty patients received 100 mg. doses and of these 48 showed negative cultures in one week. This is a 96 per cent cure rate.

When the organism was found to be resistant in vitro to furadantin a greater number of sterile urines were obtained with the 100 mg. dosage after 7 days of treatment. One hundred and seventy-four cultures were found to be resistant

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Read at annual meeting, North Central Section of American Urological Association, Cleveland, Ohio, October 3-5, 1956.

Supported by a grant from Eaton Laboratories.

The outstanding qualities of seromycin are its high solubility and rapid absorption before reaching the lower intestinal tract The chief naturally resistant bacteria are Pseudomonas, Proteus and Streptococcus faecalis All other common bacteria of the urinary tract are sensitive or partially so In general it has been our experience that the development of bacterial resistance during therapy has been slower than to any other available antibiotics

The side reactions to seromycin in general have occurred only when the blood level is greater than 30 micrograms per cubic centimeter which seldom occurs in adults on 500 mg or less daily We have administered more than 4,000 gm during the past 2 years and only occasionally has the drug had to be discontinued on 500 mg daily and never on 250 mg daily We have not seen any dermatologic manifestations but a few have been reported chiefly on the higher dosage There has not been a single known instance of diarrhea, perianal pruritus, vulvar or vaginal irritation in our series I believe that prophylactic or long-term administration is indicated in certain types of chronic and recurrent infections, as seen more commonly in women and girls, after it has been demonstrated that there are no contributing lesions in the urinary tract Also, in muscular atonicity and in some instances of neurogenic stasis, long-term administration is beneficial Because of its tolerance in small dosage over long periods, seromycin has proved quite satisfactory However, it should be emphasized that there are other medicaments suitable for the above purpose Recently Marshall and Johnson[2] reported on a series of children to whom furadantin had been administered with imposing success to prevent recurrence The duration of therapy was from seven up to 16 months They found that these infections could be controlled on as little as two to three mg per kg of body weight About a year ago I[3] reported that 50 mg four times daily was usually sufficient to cure acute infections, particularly in women There are other prophylactic agents of value in selected instances such as mandelamine and sulfonamides although the latter is limited by the tendency of the bacteria to develop resistance or the patient to become sensitized to it

The preliminary results are encouraging in the treatment of tuberculosis by a combination of seromycin, 250 mg twice daily, and isoniazid, 150 mg twice daily, but many more observations are needed before final evaluation Uncomplicated acute cystitis in women and other like infections are eradicated quite promptly with 250 mg of seromycin administered twice daily Seromycin, combined with other agents in half dosage, for chronic infections would seem to be a safe and logical procedure but the optimum combinations for the various bacteria have not as yet been determined

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[2] Marshall, Matthew, Jr , and Johnson, III, S H Treatment of chronic urinary tract infection in children with nitrofurantoin J Urol , 76 123-128, 1956

[3] Herrold R D Antimicrobial agents for urinary infections and some new concepts J Urol , 75 892-899, 1956

TABLE 5 *One organism on culture*

No Patients	Dosage	Neg Culture	Cure Rate
70	50 mg	60	85%
46	100 mg	37	81%
116 Total		97	

TABLE 6 *Two organisms on culture*

No Patients	Dosage	Neg Culture	Cure Rate
33	50 mg	17	51%
17	100 mg	10	59%
50 Total		27	

TABLE 7 *Three organisms on culture*

No. Patients	Dosage	Neg Culture	Cure Rate
11	50 mg	4	38%
10	100 mg	4	40%
21 Total		8	

TABLE 8

	Number Sensitive	Number Resistant
Strep faecalis	38	21
* Coli aerogenes	30	23
† E coli	16	7
Ps aeruginosa	8	42
† E intermedium	6	0
Hemolytic Staph aureus	4	2
Proteus mirabilis	3	17
Proteus rettgeri	0	7
† Aerobacter aerogenes	5	14
Atypical pseudomonas	1	14
† Klebsiella pneumoniae	0	6

* The 53 organisms listed in the Coli aerogenes group were not identified further

† These organisms were not included in the Coli aerogenes group

mg as readily as to 100 mg dosage However it was seen that gram-positive resistant organisms responded better to the larger dosage (table 4)

Of these 188 patients, 116 were found to have urine cultures showing a pure strain of a single organism (table 5) Ninety-seven of these patients had sterile urine after 1 week's treatment regardless of the gram stain Seventy patients received 50 mg 4 times daily with 60 negative cultures giving a cure rate of 85 per cent Forty-six patients received 100 mg 4 times daily with 37 negative cultures giving a cure rate of 81 per cent

Of the 188 cases, 50 were found to contain 2 organisms 27 of these patients

TABLE 1 *Sensitive in vitro cases*

No Cultures	Dosage	Neg Cultures	Cure Rate
77	50 mg	73	94%
50	100 mg	48	96%
127		121	94 4%

TABLE 2 *Resistant in vitro cases*

No Cultures	Dosage	Neg Cultures after 7 Days	Cure Rate
95	50 mg	55	58%
79	100 mg	50	64%
174		105	60%

TABLE 3 *In vitro resistant cultures according to Gram stain*

	No Cultures	Resistant	% Resistant
Gram pos	77	27	35%
Gram neg	221	147	66%

TABLE 4 *Gram negative organisms*

Dosage	Resistant	Sensitive
50 mg	58% Cure	93% Cure
100 mg	57% Cure	93% Cure

Gram positive organisms

Dosage	Resistant	Sensitive
50 mg	53% Cure	97% Cure
100 mg	100% Cure	100% Cure

in vitro to furadantin (table 2) Ninety-five received 50 mg 4 times daily with 55 negative cultures after one week's treatment, a cure rate of 58 per cent Seventy-nine received 100 mg 4 times daily with 50 negative cultures, a cure rate of 64 per cent

We should emphasize that more than one culture was taken on a good many patients, hence there will be more cultures tabulated than there were patients

Gram stains were run on all cultures and it was found that gram-negative organisms were generally more resistant than gram-positive in vitro (table 3) A total of 77 cultures showed gram-positive organisms with only 27 resistant in vitro A total of 221 cultures showed gram-negative organisms with 147 resistant to furadantin *in vitro* The percentage of gram-negative ones showing resistance was thus nearly double that of the gram-positive ones

But while gram-negative organisms showed a higher resistance in vitro to furadantin then did gram-positive organisms, they responded clinically to 50

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SULFAETHYLTHIADIAZOLE (SETD)* THERAPY FOR SIMPLE AND COMPLICATED URINARY TRACT INFECTIONS

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From time to time, new antibacterial agents become available that, because of certain pharmacologic properties, appear to offer advantages over drugs currently being used One such drug, sulfaethylthiadiazole (SETD), was recently made available to us Based on reports of others,[1] [2] [3] SETD should be of value in treating infections of the urinary tract since it produces excellent blood and urine concentrations and is effective against most of the gram-negative and gram-positive pathogenic organisms that repeatedly invade this system Moreover, since reports indicate that the drug undergoes less than 10 per cent acetylation (inactivation) in body fluids and that 200 to 300 mg per cent of the drug is soluble in urine, SETD should offer a wide margin of safety when used clinically

Before a study was undertaken to determine the value of SETD in treating simple and complicated infections of the genitourinary system, it seemed advisable to confirm the data already reported for blood and urine concentrations and urinary recovery

MATERIAL

Two dosage forms of the drug were used during the investigation, a tablet containing 0 5 gm SETD, and a sustained release preparation† containing 13 gm per cc In the latter form, SETD is present as thousands of micropellets suspended in a fruit-flavored vehicle After being ingested, the micropellets release a sufficient amount of SETD to produce therapeutic concentrations (8–15 mg per cent) of the drug in the blood The remaining SETD is released from the micropellets over the next 10 hours, maintaining therapeutic concentrations in the blood for 12 hours

METHOD AND RESULTS

Laboratory Blood concentrations of SETD were measured in two separate groups of volunteer subjects every 2 hours for a period of 12 hours One group received a single 4 0 gm dose of the drug in tablet form, the other group received one 4 0 gm dose in sustained release form Urinary excretion of the drug was

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* N1 (5-ethyl 1,3-4 thiadiazol 2 yl) sulfonilamide

[1] Foltz, E L, Swintosky, J V and Robinson, M J Absorption, distribution, and fate of sulfaethylthiadiazole administered orally and intravenously Fed Proc 15 422, 1956

[2] Frisk, A Rune Sulfanilamide derivatives Chemotherapeutic evaluation of N′ substituted sulfanilamides Acta med Scand (Suppl 142) 1–199, 1943

[3] Rhodes, R E and McCaughan, J Sulfaethylthiadiazole In vivo and in vitro evaluation, in press, Antib Chemo

† Marketed by Smith, Kline and French Laboratories as 'Sul Spansion'

had a negative culture after 1 week's treatment (table 6) Thirty-three patients received 50 mg 4 times daily with 51 per cent cured Seventeen patients received 100 mg 4 times daily with 59 per cent cured

In 21 patients the culture contained 3 organisms (table 7) Only 8 of these had a negative culture after 1 week's treatment regardless of the size of the dose of furadantin Eleven patients received 50 mg 4 times daily with 38 per cent cured Ten patients received 100 mg 4 times daily with 40 per cent cured

In one patient 4 organisms were isolated on the culture This patient did not respond to 100 mg furadantin 4 times daily for 1 week

Five patients who proved to have Trichomonas infestation were not included in these tabulations

The various organisms found and their in vitro response to sensitivity tests are listed in table 8

SUMMARY

One hundred eighty-eight patients with urinary tract infections were studied Comparison of the results obtained when using 50 mg or 100 mg furadantin 4 times daily for 7 days has been made The larger dose was necessary only for resistant strains of gram-positive organisms

Results have been tabulated and presented in three categories

Group 1 Those sensitive or resistant in vitro to furadantin

Group 2 Comparison of gram-negative and gram-positive organisms, in regard to in vitro sensitivity

Group 3 The number of organisms cultured in each case

The percentage of negative cultures was highest when only 1 organism was present, regardless of the dosage used When 2 organisms were found the number of negative cultures after 1 week's treatment was 54 per cent When 3 organisms were found to be present, the percentage of negative cultures was only 38 per cent, regardless of the size of the dose The greatest difference in the rate of cure was found to be in the cases of gram-positive resistant in vitro organisms In this group only 53 per cent were found free of infection after 1 week of 50 mg 4 times daily The patients receiving 100 mg in this group resulted in 100 per cent negative cultures after 1 week's treatment

CONCLUSION

There is no difference in the cure rate of gram-negative organisms, either sensitive or resistant in vitro, to 50 mg or 100 mg furadantin q i d for 1 week

There was a difference in response of gram-positive resistant in vitro organisms to 50 and 100 mg dosage

With the above exception this study seems to show that 50 mg furadantin 4 times daily is just as effective as 100 mg in the treatment of urinary tract infections

$2\frac{1}{2}$ hours of the 12 hour measurement period The smaller amount of acetylation observed when the sustained release dosage form was given may have been due to the slow, continuous absorption of the drug from the gastrointestinal tract

Urinary concentration, recovery, and acetylation of SETD for a 96 hour period following a 13 65 gm dose of the drug in sustained release form given over a 60 hour period are shown in table 1 The average urinary concentration of SETD was 212 35 mg per cent

Of the total administered dose 90 16 per cent was recovered as free SETD, 3 18 per cent was recovered in the acetylated form Blood and urine concentrations and urinary recovery data obtained in these experiments agree with those previously reported

Clinical Over 100 patients, almost all of whom were outpatients, with simple or complicated infections of the urinary tract were treated with SETD This report is based on clinical results observed in 75 patients (23 woman and 52 men) who had sufficient therapy and followup examinations, both urological and bacteriological, to permit an adequate evaluation of the drug

The diagnoses of patients treated for urinary tract infections were based on symptomatology, physical findings, urinalyses, urine cultures, and results of cystoscopic and radiologic examinations Pyelonephritis, cystitis, postoperative prostatectomy with pyuria, urethritis, and epididymitis were most frequently observed Many of these conditions were complicated by obstruction and other factors

After a history and physical examination were completed on each patient, a urine specimen was collected for routine analysis and bacterial culturing Additional urine specimens were collected from each patient during and upon completion of therapy A final urine specimen was collected after drug therapy had been discontinued for at least 1 week Cultures were examined following 24 hours of incubation and organisms, if present, were identified Subcultures of the organisms were made for sensitivity testing

Disc and tube-dilution methods of testing sensitivity of bacteria to SETD were carried out simultaneously on approximately half of the isolations to determine the reliability of the disc method Filter-paper discs containing SETD were placed on blood agar plates, the surface of which had been inoculated with a diluted (1 10) 18–24 hour broth culture of the organism Tubes of trypticase soy broth containing two-fold concentrations of SETD were inoculated with 0 1 cc of 18–24 hour broth culture diluted 1 1,000,000 Inhibition of growth was determined following overnight incubation Since results of bacterial sensitivity obtained with both methods were essentially the same, the more practical disc method was used throughout the remainder of the study

Fifty patients received 1 0 gm (2 tablets) of SETD 4 times daily Twenty-five patients received 2 tablespoonfuls (30 cc, or 4 0 gm) of the sustained release preparation initially, and 1 tablespoonful (15 cc, or 2 0 gm) every 12 hours Clinical improvement was evaluated by the disappearance of symptoms improvement observed on physical examination and by the return to normal of the patient's urine

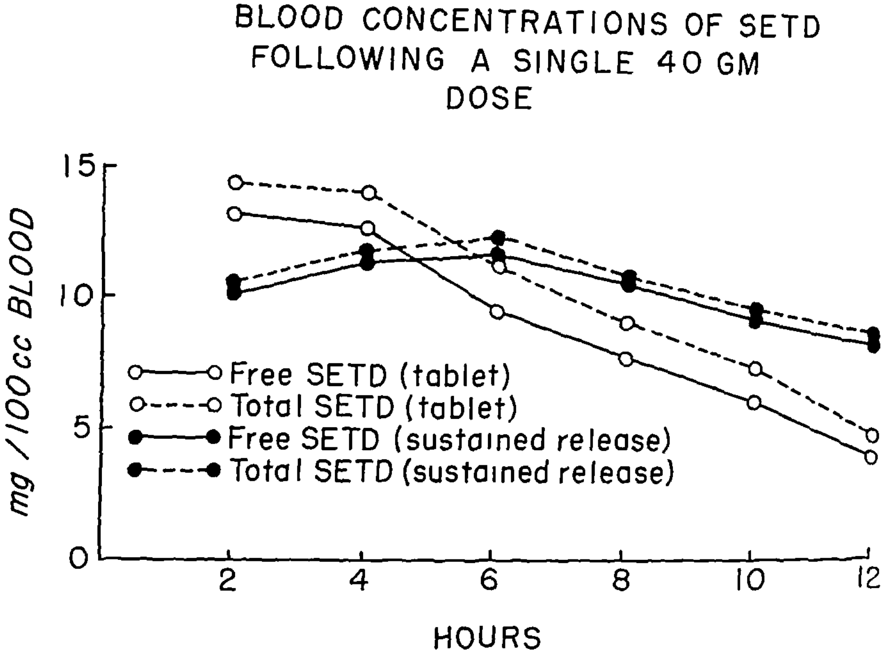

Fig 1

Table 1 *96 hour urinary recovery of SETD following 13 65 gm dose in sustained release form*

Subject	Ml Urine Excreted	Mg SETD Excreted		Urinary Concentration of SETD	Dose Excreted	Excreted SETD Acetylated
		Free	Total			
				mg per cent	*per cent*	*per cent*
B V *	7,050	11,486	11,839	162 9	84 1	2 6
N L *	4,615	13,027	13,414	282 3	96 4	1 9
F P	6,875	12,807	13,110	186 3	93 8	2 2
R G	6,909	12,814	13,600	185 5	93 9	5 7
H F	5,530	12,297	12,654	222 4	90 1	2 6
J P	4,810	11,290	11,845	234 7	82 7	4 1
Averages	5,965	12,287	12,744	212 35	90 16	3 18

* Females

measured after subjects had been given the sustained release preparation of SETD every 12 hours for 60 hours (total dose 13 65 gm), urine was collected for 96 hours Blood and urine were analyzed for free and total (free plus acetylated) SETD according to the Frisk modification of the Bratton-Marshall method [2]

Blood concentrations of SETD produced by a single 4 0 gm dose administered in tablet and sustained release dosage forms are shown in figure 1 Blood concentrations produced by the sustained release form are consistently within the accepted therapeutic range 8–15 mg per cent), while those produced by an equivalent tablet dose tend to fall below the therapeutic range during the last as are all sulfonamides in treating urinary infections complicated by obstruction or other factors SETD seems to be useful as adjunctive therapy while other urologic procedures are being carried out

The large percentage (80 per cent) of micrococci sensitive to SETD is particularly noteworthy since this group of bacteria has shown the greatest propensity towards becoming drug resistant Of importance too because they possess a natural resistance to most antibacterial agents is the number of organisms belonging to the genus Pseudomonas that were sensitive to SETD

Clinical results in this series of patients indicate that blood concentrations produced by SETD are sufficient to control infections present in the tissues and that urine concentrations are adequate for antibacterial activity in the urine

The advantages of the sustained release preparation seem to be 1) continuous antibacterial activity due to prolonged relatively constant therapeutic blood and urine concentrations 2) fewer chances of ambulatory patients missing doses since the drug need be taken only twice daily and 3) no need of waking ill patients during the night to administer medication

SUMMARY

Over 100 patients were treated with SETD for simple and complicated infections of the urinary tract Seventy-five patients (23 women, 52 men) returned to the clinic a sufficient number of times to permit an adequate evaluation of the drug

Fifty patients received SETD in 0 5 gm tablets The remaining 25 patients received a sustained release preparation of SETD Of the patients with simple infections of the urinary tract 91 per cent showed a good response 63 per cent of the complicated urinary infections also responded to SETD therapy No serious side effects were observed during treatment

Results of testing bacterial sensitivity to SETD by tube-dilution and disc methods were generally equivalent

The unusually large number of micrococci sensitive to SETD is noteworthy since this group of organisms has shown the greatest tendency towards becoming drug-resistant

While the results of treatment with both dosage forms are essentially similar the relatively infrequent administration of the sustained release dosage form represents an advantage in the treatment of ambulatory patients

The authors are indebted to Miss Barbara Vale for her technical assistance

TABLE 2. *Clinical response to SETD in tablet and sustained release dosage forms*

Diagnosis	Clinical Response with Tablet SETD				Clinical Response with Sustained Release SETD				Total No. Treated
	Simple Infections		Complicated Inf.		Simple Infections		Complicated Inf.		
	Good	Poor	Good	Poor	Good	Poor	Good	Poor	
Post op. prostatectomy	12	1	5	2	4	1	0	2	27
Cystitis	9	1	5	0	4	0	2	0	21
Pyelonephritis	4	0	1	3	5	0	0	0	13
Prostatitis	0	0	1	2	0	1	1	1	6
Epididymitis	0	0	1	0	1	0	1	0	3
Urethritis	1	0	1	1	1	0	1	0	5
	26 (92.8%)	2	14 (63.6%)	8	15 (88.2%)	2	5 (62.5%)	3	75

TABLE 3. *Sensitivity of organisms* isolated from urine specimens to sulfaethylthiadiazole*

Organisms	Number of Isolation	Sensitivity to Sulfaethylthiadiazole
Coliform bacilli	40	27
Micrococci	30	24
Pseudomonas	10	6
Enterococci	14	6
Proteus	5	2
Diphtheroides	4	3
Totals	103	68

* Based on isolations from 90 different patients.

Results of treatment with SETD are shown in table 2. Of the 45 patients who received SETD for simple infections of the urinary tract, 41 (91 per cent) showed a good response to therapy. Although results obtained in patients with complicated infections indicate that the presence of foreign bodies and other complicating factors interfered with the effectiveness of the drug, an unusually high rate of improvement (63 per cent) occurred. One patient who received the sustained release suspension complained of nausea and gastric upset which may or may not have been related to the drug. Serious side reactions, such as hematuria and renal blockage, were not observed during or after therapy in any of the patients. A sensitization reaction to the drug was observed in a patient who was known to be allergic to other sulfonamides. The average length of treatment for simple infections was 7 days, for complicated infections, 12 days.

The sensitivity of organisms isolated from patients' urine to SETD is given in table 3.

DISCUSSION

As judged from the response of patients seen during the present study, SETD is useful in treating simple infections of the urinary tract. Although less effective,

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CARDIAC ARREST DURING UROLOGIC PROCEDURES

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A recent case of cardiac arrest during transurethral prostatectomy in our practice prompted us to review the literature on this subject Although there are cases reported during a variety of surgical operations, we were surprised at the almost complete lack of reference to cardiac arrest during urologic procedures All urologists have a knowledge of this dramatic problem, but certainly not all have a working understanding or a routine for its care should such a drastic emergency arise [1 3]

Cardiac arrest, by definition, is the unexpected, sudden onset of cessation of cardiac output As a surgical emergency it takes precedence over all others, for death, or permanent irreparable cerebral damage ensues if the brain is deprived of adequate oxygenation for a period exceeding approximately four minutes Resuscitation beyond this time limit can scarcely be deemed successful, even if the patient survives, because almost without exception, it is a vegetative decerebrate existence

This problem is not new, rather it is a problem which has existed since shortly after the first use of general anesthesia, and one that is being attacked continuously with increased vigor in research, in practice and in publicity Hosler's[4] calculation of 10,000 cardiac arrests occurring annually in the United States gives added impetus to the search for more efficient methods of prevention and recognition, and more successful treatment of this catastrophe The incidence of cardiac arrest is felt by some investigators to be increasing Briggs et al ,[5] in a series covering 189,815 anesthetic and surgical procedures from 1925 to 1954, reported an overall incidence of operating room deaths of 1 1091, and of cardiac arrests of 1 1406 The incidence in the first two decades was 1 2458, and from 1945 to 1954, a total incidence of 1 1038 They conclude that cardiac arrest is the major single cause of death in the operating room, and that there has been an absolute increase in the incidence of cardiac arrest in recent years Table 1 shows the incidence of cardiac arrest and recovery rate from reports by several authors

ETIOLOGY

The etiologic factors of prime importance are hypoxia (lack of oxygen) and hypercapnea (excess of carbon dioxide) Several excellent reports by experi-

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Read at annual meeting North Central Section of American Urological Association, Cleveland Ohio October 3–5 1956

[1] Dale W A Cardiac arrest Ann Surg 135 3, 1952

[2] Snyder W H Snyder M H and Chaffin L Cardiac arrest in infants and children A M A Arch Surg 66 714 1953

[3] Barrett W A , Green, J R , Heinrich A N and Uram, H Three minutes in cardiac arrest J Int Coll Surg , 20 6 1953

[4] Hosler R M Manual on Cardiac Resuscitation Springfield, Ill Charles C Thomas, publisher 1954

[5] Briggs B D Sheldon D B and Beecher H K Cardiac arrest J A M A , 160 17,

of surgery, are likely prospects for cardiac arrest and should be evaluated preoperatively The life span of man is increasing yearly and with this added longevity, cardiovascular disease assumes increased importance Genitourinary problems, too, become more prominent in this older age group Therefore, it is logical to assume that the individual physician responsible for the management of these genitourinary problems must be cognizant of the patient's cardiovascular-respiratory status as well as the urological status Certain preoperative determinations such as vital capacity, venous pressure and circulation time are helpful Determination of the patient's serum potassium, sodium, chloride, and carbon dioxide levels prior to surgery provides additional information Arterial oxygen saturation when indicated can be obtained Predisposing factors also worth considering are 1) Preoperative medication Large doses of narcotics, with their effect of respiratory depression, should be avoided, since they may further impair ventilation in an individual possibly having chronic hypoxia of some degree 2) Atropine in sufficient amount, and in proper time relationship to the actual anesthetic procedure, is an aid in controlling abnormal vagal responses and also diminishes bronchial secretions 3) Position of the patient during procedure Positions which may interfere with adequate oxygenation should be avoided, or if such position is absolutely necessary, particular attention must be given to insure proper obstruction-free respiratory exchange by endotracheal intubation

DIAGNOSIS AND TREATMENT

Bradycardia and falling blood pressure in an anesthetized individual, with a previously normal pulse and blood pressure, are signs of progressive asphyxia and impending cardiac arrest Immediate check must be made to insure that oxygenation is adequate, and that respiratory excursion is sufficient to correct, or prevent, hypercapnea Cardiac arrest is present when blood pressure and pulse are unobtainable From the moment this occurs, the patient has only four critical minutes if he is to be retrieved with any significant degree of success Time should not be wasted by futile motions looking for stethoscopes to listen for heartbeat, searching for medications and the equipment to inject them into the heart, and by calling for more adequately trained personnel to perform thoracotomy and cardiac massage As time flies the neuron dies[9] The responsibility rests with the surgeon, or the individual most capable to perform thoracotomy and cardiac massage As urologic surgeons, we must be ever aware of our duty in this regard, and must be prepared to deal with this situation promptly and intelligently Provided sterile thoracotomy instruments are present, they are used, but all that is absolutely essential is a scalpel Skin asepsis is a matter of little importance at this time An incision is made medial to lateral in the left fourth or fifth interspace, with several quick strokes of the blade This approach permits more efficient cardiac massage, and is considered vastly superior to the transdiaphragmatic route Laceration of the lung can be avoided

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[9] Turk, I N and Glenn, W W L Cardiac arrest Results of attempted cardiac resuscitatio[illegible] cases New Eng J Med , 251 795–803, 1954

TABLE 1*

Author	Location	Reported Arrests	Total Cases and Length of Time	Arrest Ratio	% of Survival
Ament	Bellevue Hosp., New York City	9	28,000 (3 yrs.)	1:3111	75
Bergner	Louisville, Ky.	17	35,000 (4 yrs.)	1:2058	64
Blades	Geo. Wash. Hosp., Wash., D.C.	4	54,579 (5 yrs.)	1:13,645	50
Bonica	Tacoma, Wash.	15	90,000 (7 yrs.)	1:6000	not stated
Briggs	Mass. Gen. Hosp., Boston, Mass.	85	189,815 (30 yrs.)	1:1406	not stated
Hanks	Presbyterian Hosp., New York City	23	49,728 (4 yrs.)	1:2162	43
Hewlett	Brooke Army Hosp., San Antonio, Texas	28	unknown (5 yrs.)	1:2949	50
Johnson	Univ. Pennsylvania Hosp., Philadelphia	19	95,000 (7 yrs.)	1:5000	52
L. A. F. B.	San Antonio, Texas	6	14,809 (2½ yrs.)	1:2468	85
Miller	University Hosp., Mpls., Minn.	14	12,000 (2½ yrs.)	1:858	not stated

* From Martin and Tarrow: Current Res. Anesth., 35: 147–164, 1956.

mental investigators have shown this to be true. Sloan[6] reported that stimulation of the vagus nerve at the hilum of the lung failed to produce arrest in adequately oxygenated dogs. Animals subjected to marked progressive hypoxia, or asphyxia, showed central cardio-inhibitory impulses which resulted in increased bradycardia and a fall in blood pressure. Under these conditions stimulation of the vagus nerve did produce additional cardiac inhibition, and frequently was followed by arrest. Cardiac arrest occurred more frequently during progressive asphyxia than during hypoxia alone. Young, Sealy, Harris and Botwin[7] report that hypercapnea enhances the effect of vagal stimulation on the heart, whereas hypoxia diminishes the effect of vagal stimulation. Stewart, Virtue and Swan[8] concluded that hypercapnea significantly enhances vagal cardiac arrest in the normal dog, but not in the chronically hypoxic dog. They also report that vagal stimulation produced ventricular fibrillation in one-third of the chronically hypoxic dogs, but not in previously normal dogs.

What is the significance of these findings in relation to cardiac arrest in patients in the urologic service? Chronic cardiovascular disease with its attendant decreased vital capacity can result in unrecognized chronic hypoxia of varying degrees in the preoperative state. Toxemia and fever, such as occur with severe urinary tract infections, anemia and inanition, are also factors which can produce a subclinical hypoxia. Patients with such problems, when subjected to the stress of surgery, are likely prospects for cardiac arrest and should be so evaluated preoperatively The life span of man is increasing yearly and with this added longevity, cardiovascular disease assumes increased importance Genitourinary problems, too, become more prominent in this older age group Therefore, it is logical to assume that the individual physician responsible for the management of these genitourinary problems must be cognizant of the patient's cardiovascular-respiratory status as well as the urological status Certain preoperative determinations such as vital capacity, venous pressure and circulation time are helpful Determination of the patient's serum potassium, sodium, chloride, and carbon dioxide levels prior to surgery provides additional information Arterial oxygen saturation when indicated can be obtained Predisposing factors also worth considering are 1) Preoperative medication Large doses of narcotics, with their effect of respiratory depression, should be avoided, since they may further impair ventilation in an individual possibly having chronic hypoxia of some degree 2) Atropine in sufficient amount, and in proper time relationship to the actual anesthetic procedure, is an aid in controlling abnormal vagal responses and also diminishes bronchial secretions 3) Position of the patient during procedure Positions which may interfere with adequate oxygenation should be avoided, or if such position is absolutely necessary, particular attention must be given to insure proper obstruction-free respiratory exchange by endotracheal intubation

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[6] Sloan, H. E.: The vagus nerve in cardiac arrest. The effect of hypercapnea, hypoxia and asphyxia on reflex inhibition of the heart. Surg., Gynec. & Obst., 91: 257, 1950.

[7] Young, W. G., Sealy, W. C., Harris, J. and Botwin, A.: The effects of hypercapnea and hypoxia on the response of the heart to vagal stimulation. Surg., Gynec. & Obst., 93: 51, 1951.

[8] Stewart, B. D., Virtue, R. W. and Swan, H.: Cardiac arrest and ventricular fibrillation. A. M. A. Arch. Surg., 66: 703, 1953.

DIAGNOSIS AND TREATMENT

Bradycardia and falling blood pressure in an anesthetized individual, with a previously normal pulse and blood pressure, are signs of progressive asphyxia and impending cardiac arrest Immediate check must be made to insure that oxygenation is adequate, and that respiratory excursion is sufficient to correct, or prevent, hypercapnea Cardiac arrest is present when blood pressure and pulse are unobtainable From the moment this occurs, the patient has only four critical minutes if he is to be retrieved with any significant degree of success Time should not be wasted by futile motions looking for stethoscopes to listen for heartbeat, searching for medications and the equipment to inject them into the heart, and by calling for more adequately trained personnel to perform thoracotomy and cardiac massage As time flies the neuron dies[9] The responsibility rests with the surgeon, or the individual most capable to perform thoracotomy and cardiac massage As urologic surgeons, we must be ever aware of our duty in this regard, and must be prepared to deal with this situation promptly and intelligently Provided sterile thoracotomy instruments are present, they are used, but all that is absolutely essential is a scalpel Skin asepsis is a matter of little importance at this time An incision is made medial to lateral in the left fourth or fifth interspace, with several quick strokes of the blade This approach permits more efficient cardiac massage, and is considered vastly superior to the transdiaphragmatic route Laceration of the lung can be avoided

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[9] Turk L N and Glenn, W W L Cardiac arrest Results of attempted cardiac resuscitation in 42 cases New Eng J Med, 251 795–803, 1954

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[6] Sloan H E The vagus nerve in cardiac arrest The effect of hypercapnea hypoxia and asphyxia on reflex inhibition of the heart Surg , Gynec & Obst , 91 257, 1950

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[9] Turk L N and Glenn, W W L Cardiac arrest Results of attempted cardiac resuscitation in 42 cases New Eng J Med 251 795-803 1954

If fibrillation is present, massage is continued for a few minutes until the color of the myocardium is improved since the anoxic myocardium tolerates electric shock poorly, and further damage could result When the color of the myocardium has improved, defibrillation is attempted by use of electric shock techniques such as those described by Wiggers[10] This form of therapy was developed following observation that passage of strong electric current through the heart produces simultaneous contraction of all the myocardial fibers Following this massive contraction the heart is in standstill while relaxation follows Spontaneous beat returns with regular rhythm after the period of asystole Single shocks delivered by means of a commercial defibrillator are used The heart is compressed between the sterile electrodes, and a shock of 110 to 130 volts and 2 amperes for 0 1 to 0 5 second may be used At times, serial shocks of short duration may be of more value than a prolonged single shock Precautions must be taken to avoid burning the cardiac muscle, and to avoid electrocution of the surgeon and other members of the resuscitation team It is advisable for all members of the team to remove their hands from the patient, and avoid contact of the patient and the operating table during the period of application of the electrodes In conjunction with the surgeon's efforts, the anesthesiologist attempts correction of asphyxia by administration of 100 per cent oxygen via endotracheal tube, or if not intubated, by a closed mask until intubation can be accomplished, and provides artificial respiration sufficient to furnish adequate respiratory exchange Whole blood replacement, rapidly, to correct circulatory volume deficit is useful However, care should be exercised to avoid overloading the circulatory system

DRUGS

Stimulants to anoxic myocardium should be avoided since they are of questionable value, and may produce additional damage However, once the condition of the myocardium has improved by massage, certain drugs may be of value

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[10] Wiggers, C J Cardiac massage followed by counter shock in revival of mammalian ventricles from fibrillation due to coronary occlusion Am J Physiol , 116 161 1933

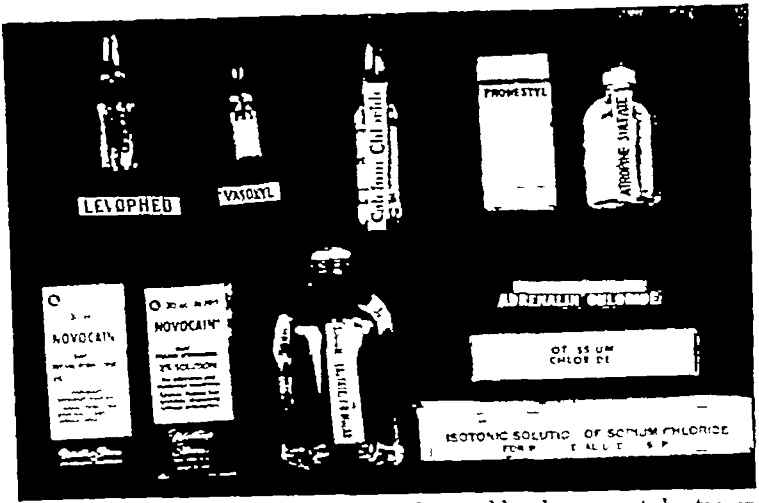

Fig 1 Drug tray with levophed, vasoxyl calcium chloride pronestyl, atropine, novocain 1 and 2 per cent sodium lactate, adrenalin, potassium chloride and isotonic saline solution Tray is on each anesthesiologist's table and is checked and ready for use before each surgical procedure

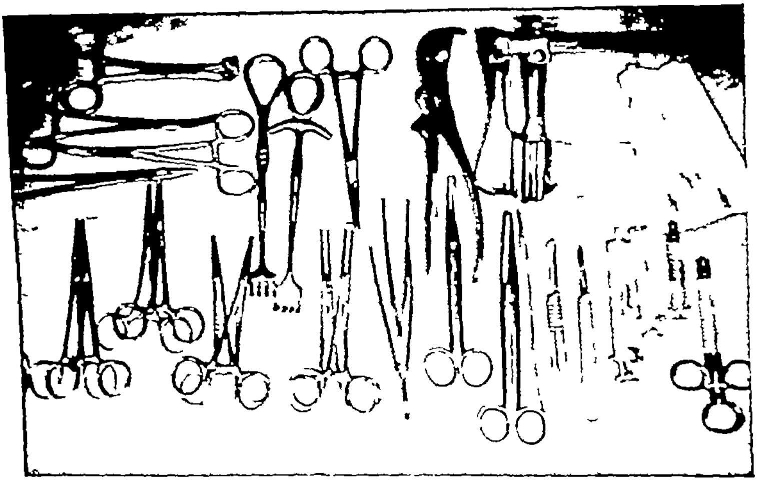

Fig 2 Contents of sterile thoracotomy set Set is wrapped in red muslin for rapid identification

These solutions are injected directly into the chamber of the left ventricle so that rapid entrance to the coronary circulation is obtained If asystole is present, 1 cc of a solution containing 1 cc of 1 1000 epinephrine diluted to 10 cc of normal saline is used, and this may be repeated in four to five minutes If this does not produce a satisfactory response, 2 to 4 cc of a 10 per cent solution of calcium chloride may be used

If ventricular fibrillation is present, the use of epinephrine, and/or calcium chloride is to be avoided since this may make the fibrillation refractory to further treatment When ventricular fibrillation is present, intracardiac procaine 100 mg

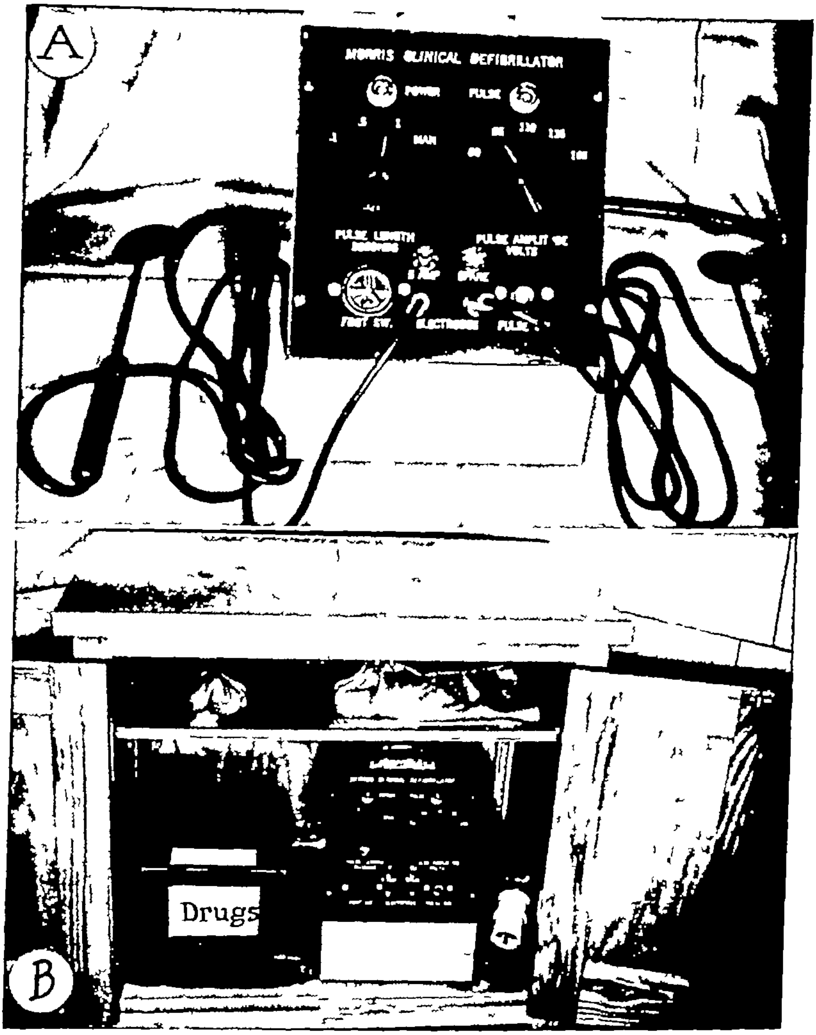

FIG 3 *A*, Morris clinical defibrillator Sterile electrodes are wrapped in red muslin rather than conventional green or white
B, thoracotomy set, sterile electrodes and defibrillator are kept in this portable cabinet

to 200 mg , or pronestyl 300 mg to 1000 mg in 2 per cent to 10 per cent solutions, should be used, accompanied by defibrillation by electric shock [11]

Vasopressors such as vasoxyl, neosynephrine, and wyamine may be useful in keeping the blood pressure above shock level Rapidly acting glucosides (cedilanid and acetyl strophanthin) may be used if spontaneous cardiac activity does not produce a peripheral pulse [12]

If resuscitation is successful, the chest is closed after approximately fifteen minutes of adequate cardiac action Massage should not be discontinued for a reasonable period of time, even if attempts are unsuccessful to restore action through the use of drugs or other methods Instances are reported in which cardiac activity returned after thirty to forty minutes of massage If effective circulation has not returned within one hour, massage may be discontinued The decision to discontinue massage should not be made on the presence of peripheral cyanosis, because a patient may still be cyanotic and have effective circulation

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[11] Martin, J T and Tarrow, A B A review of cardiac resuscitation Current Res Anesth , 35 147-164 1956

[12] Sadove, M S , Wyant, G M Julian O C and Dye, W S Cardiac arrest Amer Surg , 20 5, 1954

From the foregoing, it becomes readily apparent that these measures can be accomplished properly only in the presence of a preconceived plan of treatment Everyone connected with anesthesia, or surgery, should understand his, or her, duties in such a crisis, and be prepared to execute these duties with machine-like precision Only through such a plan, and by periodic practice will lives be saved, which otherwise would have been lost The necessary equipment and drugs must be immediately accessible, and must be in proper working condition at all times The equipment used in one of our hospitals is shown in figures 1 to 3 and is ready for each operation before it begins

CASE REPORT

The case which prompted our study of this problem was that of a 73-year-old white, retired policeman (case 228443) in acute urinary retention admitted to St Mary's Hospital on June 24, 1955 He gave a history of symptoms of progressively increasing vesical neck obstruction for 2 years, especially pronounced the 6 months before hospitalization Acute urinary retention developed 48 and 24 hours prior to admission, relieved by catheterization by his physician There were no positive cardiovascular symptoms A peptic ulcer in 1947 was treated medically with prompt relief, and with no recurrence of symptoms Positive physical findings were limited to the genitourinary system Rectal examination revealed a two plus enlargement of the prostate gland The gland was hard, nodular, irregular, and fixed with induration extending to the seminal vesicles The lungs were clear to auscultation and percussion The heart on physical examination was normal in size with regular rhythm, and an apical pulse of 82 Blood pressure was 140/80 Excretory urography revealed architecturally and functionally normal kidneys and ureters bilaterally, and the bladder floor was moderately elevated by the prostatic enlargement Chest x-ray showed the presence of calcific deposits in the left hilar region, and a diffuse, moderate prominence of bronchovascular markings in both lung fields Admission urinalysis obtained at the time of vesical decompression contained four to six leukocytes and twelve to fifteen erythrocytes per high power field The alkaline phosphatase was 3 6 King-Armstrong units The acid phosphatase was 1 2 Bodansky units with a prostatic fraction of 0 6 The blood urea nitrogen was 14 mg per cent The hemoglobin was was 16 9 gm and the leukocyte count 10,200 with a normal differential The electrocardiogram was interpreted as normal except for mild left axis deviation

The patient's condition appeared satisfactory for surgery by the consulting internist, and on June 27, 1955 he was taken to surgery for a transurethral prostatic resection Blood pressure before anesthetic induction was 190/80 Preoperative medication consisted of subcutaneous sodium luminal, gr 2 at 6 30 a m and subcutaneous morphine sulfate gr ⅛ and atropine sulfate gr 1/200, given at 7 00 a m The anesthetic, intravenous 2 5 per cent pentothal sodium solution containing 5 mg per cc flaxedil, supplemented by nitrous oxide and oxygen, using the semiclosed technique began at 8 40 a.m Induction was satisfactory, and resection of the prostate began at 8 50 a m There was moderate amount of prostatic bleeding which was controlled with moderate difficulty because of the sclerotic character of the vascular supply of the prostate and administration of 500 cc of whole blood was started slowly at 9 05 a m The blood pressure and pulse remained stable from the beginning of the procedure until 9 22 a m at which time the patient became cyanotic The anesthetic was immediately discontinued, and an endotracheal tube was inserted at 9 25 a m at which time cardiac arrest was noted Thoracotomy was accomplished within three minutes Asystole was present, but after massage for 1 minute active, regular, quite forceful contractions appeared at a rate between 60 to 70 per minute These persisted for 3 minutes and then ceased Additional massage was applied, but cardiac action, except for a few incompetent contractions at rare intervals, could not be restored It was possible to maintain the systolic blood pressure at 90 mm mercury, but in spite of this and forced respiration with 100 per cent oxygen concentration, there was no improvement in the patient's color at any time Cardiac massage was maintained for 45 minutes The defibrillator was used twice during this period without ever restoring cardiac action The patient was pronounced dead at 10 20 a m

At autopsy, the heart weighed 460 gm and revealed moderate left ventricular hypertrophy and patchy atherosclerosis of the coronary vessels However, the major vessels were not significantly narrowed The lungs showed no significant gross abnormalities, other than slight apical fibrosis on the left Microscopic section of the lung revealed interstitial fibrosis The final diagnosis was 1) cardiac arrest, clinical, 2) carcinoma of the prostate with extension to the seminal vesicles, 3) interstitial fibrosis, pulmonary, etiology undetermined

DISCUSSION

This appears to be a case of true cardiac arrest with pulmonary fibrosis as a possible predisposing factor Although this patient had no clinical findings or symptoms of cardiorespiratory disease prior to surgery, one wonders if the pulmonary fibrosis, although not marked, was sufficient to diminish his vital capacity and produce a chronic hypoxia of some degree before the operation Determination of this patient's vital capacity, venous pressure, and circulation time may have provided information to alert us to the possibility of cardiac arrest arising during the course of the surgical procedure Since clinical and experimental evidence shows the incidence of cardiac arrest to be significantly greater in individuals with chronic hypoxia, it is well to consider the possibility of this situation existing in the older patient even in the absence of significant preoperative symptoms or clinical findings

SUMMARY

The problem of cardiac arrest is discussed and its relation to chronic hypoxia and hypercapnea is stressed

The possibility of chronic, unrecognized hypoxia due to cardio-respiratory disease in the older patient with genitourinary problems is cited

The salient features in the diagnosis and treatment of this condition, and the responsibility of the urologist as part of the resuscitation team are pointed out

A case of cardiac arrest with chronic pulmonary fibrosis as a possible factor in the production of chronic hypoxia is described

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THE MANAGEMENT OF WILMS' TUMOR AS DETERMINED BY NATIONAL SURVEY AND REVIEW OF THE LITERATURE

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Considerable confusion and disagreement concerning the management and treatment of embryoma of the kidney (Wilms' tumor) in infancy and childhood prevail not only among the urologists but also among the other members of the medical profession, i e , pediatricians, pediatric surgeons, general practitioners, internists, radiologists, etc This situation is particularly distressing to the urologists entrusted with the teaching of medical students, and the training of urological interns and residents

In an attempt to clarify this situation, the author composed a comprehensive questionnaire which was sent to 750 members of the American Urological Association and 54 members of the Section on Surgery of the American Academy of Pediatrics residing in the United States, Canada, Mexico and the Philippines The purpose of this questionnaire was to obtain sufficient data to permit the development of an acceptable plan of management and treatment of these tumors based on 1) an evaluation of the present diagnostic methods 2) an analysis of the results obtained with the different methods of treatment and 3) a determination of the various factors influencing the survival rate

Before proceeding to an analysis of the replies to this questionnaire, the author desires to state that he is fully cognizant of the limitations and shortcomings of this method of obtaining accurate and complete information It is quite true that the data obtained are likely to be incomplete or inaccurate for any one or more of the following reasons 1) a natural reluctance to report unsatisfactory results, 2) lack of co-operation or an unwillingness on the part of the surgeon to collect the data, 3) lack of adequate clerical help to search out the necessary information, 4) accurate histories and followup records are not always available, and 5) some surgeons receiving the questionnaire have little or no experience with Wilms' tumor The objection has been raised by some that a survey based on a collection of small or large series of cases does not give a true picture of the prevailing practices or results for the reason that the same standards of diagnosis, treatment and evaluation of results are not used by all surgeons The same objection has been offered regarding surveys based on other surveys Not infrequently surveys or reports of small or large series of cases are limited in their scope because of the surgeon's particular interest in some special aspect of the subject

No one can deny the great value of reports of large series of cases from large clinics and special hospitals where the treatment is carried out by one or more specially trained surgeons according to a definite plan of diagnosis and treatment as compared to isolated reports of single or small series of cases by the average

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surgeon However it must be borne in mind that the vast majority of cases of Wilms' tumor are treated by the average urological surgeon working in a small or average sized hospital unaffiliated with a medical school Certainly such surgeons need and welcome the guidance derived from the more experienced surgeons

ANALYSIS OF DATA

A total of 126 replies were obtained, viz , 116 from urologists and 10 from pediatric surgeons Accurate and complete data were furnished by 75 urologists and 6 pediatric surgeons The necessary data were not available to 10 urologists and 2 pediatric surgeons but these men were kind enough to co-operate to the extent of expressing positive opinions wherever possible It is interesting to note that 25 urologists and 2 pediatric surgeons replied that they had no experience with Wilms' tumors which may be explained by the fact that either Wilms' tumors were not encountered in their practice or else were treated in special hospitals in their communities An inability to furnish data because of unavailability of records or lack of competent clerical help was stated by 9 urologists and 2 pediatric surgeons

INCIDENCE

A total of 856 cases were reported by 81 surgeons The condition was unilateral in 844 cases and bilateral in 12 cases (1 4 per cent) The latter figure is slightly lower than that reported by Creevy and Reiser who collected 28 cases and noted an incidence of about 2 per cent in 1170 cases In 1954 Scott collected 32 cases of bilateral tumors and added 1 case The author has collected 11 additional cases not included in the latter's series, viz , Johnson and Marshall 4, Fenney et al 3, Creevy and Reiser, DeVries, Goodwin, and Berman one each respectively

The tumors involved the two sexes with about equal frequency Both kidneys were likewise involved with equal frequency From the replies, neither kidney appeared to be a more favorable site from the viewpoint of survival after operation The condition is observed more frequently in the white than the Negro race

In this study the majority of cases occurred in the first four years of life, the average age was 3 2 years Several surgeons reported cases seen within one month after birth Although cases have been reported in the fetus and newborn, none were encountered in this series A Wilms' tumor in an adult was noted by three different observers Eserskу et al (1947) have collected 59 cases of Wilms' tumor in the adult

The familial occurrence of Wilms' tumor is rare Maslow has reported 3 cases and a possible fourth in one family and cited Bobbi as having encountered 3 cases in one family Chapian has described the condition in two brothers who died within 7 months after surgery Fitzgerald and Hardin reported a Wilms' tumor occurring in a father and two children, being bilateral in one child DeVries noted a unilateral tumor in a 3-year-old female and a bilateral tumor in her 4-year-old brother Gaulin has observed simultaneous tumors in identical twins

SYMPTOMATOLOGY

The classical triad of symptoms tumor mass, pain, and hematuria, usually associated with renal neoplasms in adults, is encountered in about 15 to 20 per cent of the cases of Wilms' tumors The incidence of the individual symptoms is reversed in Wilms' tumor of infancy and childhood The most common symptom is a palpable tumor mass in the upper abdominal quadrant or loin in 85 per cent The mass is usually detected by the mother while bathing the child or by the physician during a routine physical examination

Pain in the lumbar or upper abdominal area is the next most common symptom and the chief complaint in about 30 per cent of the other children Hematuria is relatively uncommon being present in only 10 per cent of the cases Urinary symptoms are mild or absent Gastrointestinal symptoms, i e , nausea, vomiting, diarrhea, abdominal distention and anorexia, may be conspicuous and often the reason for consulting the physician or pediatrician Other constitutional symptoms, i e , fever, loss of weight, anemia, are also not uncommon Hypertension is relatively uncommon and occasionally is relieved by surgery, according to Daniels and Bradley The mechanism responsible for this change is the pressure of the tumor tissue on the renal pedicle or intravascular elements in a manner similar to that observed in Page's cellophane perirenal bag experiments

The average duration of symptoms from the onset of the condition to the establishment of the diagnosis is difficult to ascertain in infants and young children but is generally between two to three months

DIAGNOSIS

One cannot emphasize too strongly the danger of considering every abdominal mass palpable in the first decade of life as a Wilms' tumor Unfortunately some pediatric surgeons and urologists insist on immediate surgery when a mass is palpable in children of this age group Such precipitous action has been shown to lead not infrequently to unnecessary operations, a needless sacrifice of conservable renal tissue and an increased operative mortality

An analysis was made of the various diagnostic methods employed by 93 surgeons Palpation was employed by 76 surgeons, excretory urography by 71 surgeons, retrograde pyelography by 61 surgeons, combined palpation, excretory urography and retrograde pyelography by 48 surgeons and combined palpation and excretory urography by only 4 surgeons The diagnosis was based solely on palpation by only 10 surgeons

The consensus of opinion in the replies to the questionnaire is that operation can be safely postponed until an accurate diagnosis is established An overwhelming majority recommended a combination of two or three methods with a decided preference for all three modalities Excretory urography has proven to be a valuable diagnostic aid as it enables the urologist to determine the functional status of the opposite, unaffected kidney However it does not sharply delineate the pyelographic changes induced by the tumor and is useless for this purpose when the tumor occurs in a non-functioning kidney Retrograde pyelography provides more accurate information particularly when the tumor occurs in a non-functioning kidney Pediatricians and general practitioners are gradually recognizing that cystoscopy and retrograde pyelography are invaluable diagnostic measures and may be safely performed in infants and children provided there is no contraindication to the use of a general anesthetic

It is interesting to note that an incorrect diagnosis was recorded in 32 cases, i e 6 relied on palpation alone and 26 on a combination of palpation and excretory urography Several surgeons, reporting relatively large series of 10 to 70 cases noted an incorrect diagnosis in as many as 2 to 6 cases Despite this high incidence of error, 76 authors indicated that they would require at least palpation and excretory urography to establish a correct diagnosis before operation

Other diagnostic procedures were employed in rare instances, i e needle biopsy 7 cases, presacral or perirenal air injection 4 cases, and translumbar aortography 1 case The information gained from the latter three tests does not justify their use

Differential diagnosis The data concerning the conditions most commonly confused with Wilms' tumor revealed the following in order of frequency, viz , neuroblastoma 55, congenital hydronephrosis 49, serous cyst of the kidney 20, polycystic disease of the kidney 18, retroperitoneal sarcoma 12, cyst or tumor of the adrenal 10, intra-abdominal tumor (spleen, liver, mesentery) 7, and ectopic kidney 1

CHOICE OF TREATMENT

The necessity for standardizing the treatment of Wilms' tumors should be apparent to all in view of the wide divergence of opinion arising from the results reported in the past 20 years. This phase of the subject was particularly emphasized in the questionnaire in the hope of obtaining sufficient data to indicate the present trends of treatment Specific and detailed information was requested concerning the five basic plans of treatment employed in the past 20 years, viz , 1) nephrectomy alone, 2) nephrectomy and postoperative irradiation, 3) preoperative irradiation and nephrectomy, 4) preoperative irradiation, nephrectomy and postoperative irradiation, and 5) radiation alone

An analysis of the methods of treatment employed by the surgeons answering the questionnaire is indicated in table 1 Their choice in order of frequency is 1) nephrectomy plus postoperative irradiation (55 authors, 379 cases), 2) preoperative irradiation, nephrectomy and postoperative irradiation (34 authors, 190 cases) 3) preoperative irradiation plus nephrectomy (24 authors, 86 cases), 4) nephrectomy alone (20 authors, 45 cases) and 5) irradiation alone (20 authors, 62 cases) From this study, it is readily apparent that several surgeons employed more than one method of treatment Irradiation alone was never the method of choice but only of necessity, being used exclusively in inoperable and bilateral cases The exact type of treatment was not accurately defined by 10 authors but included an exploratory operation with or without a biopsy and was either preceded or followed by irradiation

The recipients of the questionnaire were asked to specify their choice of treatment in view of their experiences and results Nephrectomy plus postoperative

TABLE 1 *Type of treatment employed in 858 cases reported by 81 different surgeons answering the author's questionnaire*

Treatment	Cases	Surgeons
1 Nephrectomy alone	45 (5 2%)	20
2 Nephrectomy plus postoperative irradiation	379 (44 1%)	55
3 Preoperative irradiation plus nephrectomy plus postop irrad	190 (22 1%)	34
4 Preoperative irradiation plus nephrectomy	86 (10 2%)	24
5 Irradiation alone	62 (7 2%)	20
6 Exploratory operation	4 (0 3%)	4
7 Exploratory operation plus biopsy plus postoperative irradiation	26 (3 3%)	5
8 No operation	19 (2 2%)	6
9 Type of operation not stated	47 (5 4%)	10
Total	858	

irradiation was the most popular with 52 surgeons, preoperative irradiation plus nephrectomy and postoperative irradiation was next with 21, nephrectomy alone was advocated by 7, and preoperative irradiation plus nephrectomy was last with 6 No author indicated a preference for irradiation alone as the method of therapy in all types of Wilms' tumor

From the data presented in table 1, it is possible to make only general deductions regarding the present trends in treatment An accurate statistical comparison of the different methods is difficult or impossible because of several unknown and many variable factors, viz , a) lack of information concerning immediate mortality and survival rate, b) individual differences in the interpretation of results, c) variations in operative technique by different surgeons employing the same basic plan of treatment, d) the unknown effect of different histological types upon operative results, and e) the effect of different dosages and duration of irradiation employed preoperatively and/or postoperatively

A brief discussion of the five basic plans of treatment is presented in order to help clarify the present situation

A) *Irradiation alone* Herman (1915) was the first to employ postoperative irradiation in the treatment of Wilms' tumor but the patient died three and a half months after the therapy was started In 1916 Friedlander, impressed with the results of irradiation in the treatment of various extrarenal neoplasms, advocated and employed irradiation as the primary treatment of renal tumors in infancy This method did not gain wide usage until the late twenties and early thirties Among the chief proponents of this method were Barringer, Dean, McNeil and Chilko, Sauer, Kerr, Portman, and others In 1934 Dean reported five survivals of 5 years in a series of 20 cases treated by irradiation alone Dramatic cures of 10-year survivals were reported by McNeal, Sauer, Nesbit and Adams, and Johnson and Garrett On the other hand, Priestley reviewed 39 cases treated in this manner prior to 1936 and failed to observe a cure in a single case Dean has recently discarded this method in favor of nephrectomy and postoperative irradiation

However, irradiation still has a limited place in the treatment of the hopelessly advanced or inoperable cases with extensive local or distant metastasis and in cases of bilateral tumors Presumptive "cures" have been reported in the presence of extensive pulmonary metastases by Kerr, Silver, and others It must be borne in mind that many tumors become radioresistant after repeated courses of irradiation

B) *Nephrectomy alone* In the latter half of the nineteenth century this method of treatment was attended by a prohibitive immediate mortality rate In 1897 Walker reported a 36 per cent mortality rate in 145 operative cases With the improvement in operative technique, anesthesia and pre- and postoperative management, a marked reduction in operative mortality resulted Ladd has been the staunchest advocate of this type of treatment In 1941 he reported 27 consecutive nephrectomies in an 8-year period with no operative deaths and 37 consecutive operations in a 13-year period with only 2 deaths (5 4 per cent) Furthermore there were 13 survivals in the series of 54 cases treated by nephrectomy alone as compared to only 1 survival in the group treated by preoperative irradiation and nephrectomy

C) *Preoperative irradiation and nephrectomy* The proponents of this method of treatment include Kretschmer, Randall, Millin, Wharton, Silvers and others The advantages claimed for this treatment are 1) irradiation causes a marked reduction in the size of the tumor and renders the operation easier in the moderate sized tumor and feasible in large or so-called inoperable tumors, 2) the resultant fibrotic changes decrease the likelihood of blood loss, spread of the tumor, and traumatic rupture of the tumor during operation, 3) during period of irradiation the general condition may be improved by judicious use of transfusion, antibiotics to combat infection, and intravenous fluids to overcome dehydration and electrolyte imbalance, and 4) in the hands of most urologists, this method has led to a reduced operative mortality and an increase in the survival rate

The opponents of this method include Ladd, Gross, Bothe, Nesbit and Adams, and others These surgeons maintain that a period of irradiation covering 2 to 4 weeks or waiting after irradiation for 2 to 8 weeks is dangerous to the patients because of the possibility of local or distant metastases occurring as a result of necrosis and liquefaction within the tumor following irradiation The validity of this view is difficult to confirm due to a paucity of histological studies of the tumor before and after irradiation and to an inability to determine with certainty the exact role of irradiation and/or surgery in the dissemination of tumor cells

Ladd and Gross and Neuhauser are of the opinion that it is possible to remove all Wilms' tumors without preliminary shrinkage

D) *Nephrectomy and postoperative irradiation* The chief advocates of this form of therapy are Ladd, Gross and their proteges In the past 5 years many urological surgeons have adopted this plan Following the report of Silvers who had obtained good results with preoperative irradiation and nephrectomy, Gross employed this method in 4 successive cases with fatal termination from metastases in each instance and abandoned this method in favor of nephrectomy and

TABLE 2 *Results of treatment of Wilms' tumor at Childrens Hospital, Boston, Mass (Gross and Newhauser)*

Time	Cases	Operative Mortality	"Cure"—2 Year Survivals		All Ages
			Below age of 12 months	Above age of 12 months	
A) 1914–1930	27	23%	42 8%	5%	4 (14 9%)
B) 1931–1939	31	0%	71 4%	20 8%	10 (32 2%)
C) 1940–1947	38	0%	80%	43 3%	18 (47 3%)

postoperative irradiation Gross advised immediate irradiation after operation while the patient is anesthetized and en route to his room

The results obtained at the Children's Hospital in Boston by Ladd and Gross over a period of 33 years are noteworthy (table 2)

Period A represents the era in which nephrectomy alone was the treatment of choice In period B Ladd used the same treatment but utilized improved surgical techniques, selective anesthesia, and better pre- and postoperative care In period C Gross introduced postoperative irradiation in the hopes of destroying residual tumor cells overlooked or missed at operation The increase in survival rate from 32 2 per cent to 47 3 per cent is striking but not conclusive, since similar high survival rates with other methods of treatment have been reported by several surgeons (Nesbit and Adams, Rusche, Silvers, Creevy, and others)

E) *Preoperative irradiation, nephrectomy and postoperative irradiation* In the past 20 years this plan of treatment has been the most widely used one and has been sponsored by Campbell, Hunt, Priestley, Rusche, Creevy and others According to Harvey, this method has yielded the highest rate of survival It appears that this method of treatment possesses the advantages of preoperative irradiation and nephrectomy (i e , shrinkage of tumor, decrease in vascularity, increase in operability, decrease in surgical hazards, etc), plus the benefits of postoperative irradiation (i e , prevention or control of local or distant metastases) It would seem that this combined procedure offers more advantages and benefits to the average surgeon who treats only an occasional case In such hands the marked degree of shrinkage of a large tumor resulting from irradiation over a period of one or two weeks has led to greater ease of operability, reduced shock and lowered mortality

F) *Other methods of treatment* Relatively few other methods have been employed in the treatment of Wilms' tumors In 1925 Foster and Mendilaharzu implanted radium twice in a patient with Wilms' tumor who was living 8 months later Coley (1935) reported a case treated by nephrectomy and postoperative administration of his serum (B prodigiosus), the patient was living and well 29 years later Neither of these methods has received popular acclaim or wide usage Recently intravenous nitrogen mustard has been used postoperatively by Burns and by Johnson and Marshall with variable degrees of benefit to the patients The latter surgeons employed this treatment in 14 cases and observed that of 10 patients living 2 years after operation, four had received nitrogen mustard Coakley (personal communication) tried colloidal radioactive gold postoperatively with no marked improvement

RESULTS OF OPERATIVE TREATMENT

The validity of answers to this question might well be challenged inasmuch as in many instances the end results were not always available nor was the type of operation clearly defined. Nevertheless, the results in 777 operative cases reported in the answers to the questionnaire are herewith presented, irrespective of the type of operative treatment, in order that one may gather some insight into the general improvement in results of the operative treatment of this condition in the past 20 years.

The most striking features of table 3 are the very low operative mortality (2.7 per cent), the very high number of patients dying within the first year (54.3 per cent) and the relatively low number of patients surviving 2 or more years. While these results are encouraging but far from satisfactory, they indicate that there has been a decided improvement in the treatment of this serious condition notwithstanding the high percentage of patients dying within the first postoperative year.

The results of the treatment of Wilms' tumor as determined by the replies to the author's questionnaire and as reported in large surveys in the literature are presented in table 4. Accurate information regarding the immediate mortality rate, the number of deaths within the first postoperative year and the number of survivals of 2 years or longer was furnished in 434 cases by 52 surgeons answering the questionnaire. In this series, the better results were obtained by preoperative irradiation plus nephrectomy plus postoperative radiation than by nephrectomy plus postoperative irradiation, as indicated by the lowered mortality rate (1.5 per cent 2 per cent), the decrease in deaths in first postoperative year (50 per cent 54.8 per cent) and the increase in 2-year survivals (25.8 per cent 15.2 per cent).

In a series of 212 cases collected from the literature between 1950–1956, those patients treated by preoperative irradiation plus nephrectomy plus postoperative irradiation had a slightly higher 2-year survival rate than those treated by nephrectomy plus postoperative irradiation (31.1 per cent 28 per cent). The difference in survival rates between the two methods is relatively slight and its

TABLE 3. *Results of 777 operative cases**

	Cases	Authors
Immediate operative deaths	21 (2.7%)	13
Died within first year	411 (54.3%)	64
Survived two years	148 (19%)	43
Survived three years	130 (16.7%)	39
Survived five years	82 (10.5%)	29
Survived ten years or more	42 (5.4%)	34
Total	834	

* There is an apparent overlapping in the results reported in this series, i.e., the difference between the 834 results reported and 777 operative cases is 57 cases. These 57 cases belong in the group of patients surviving 3 years or more and some of these patients have already been included in the group of 2 year survivals.

TABLE 4 *Results of operative treatment of Wilms' tumor as determined from authors' questionnaire and surveys in literature*

	Abeshouse (1956) 434 Cases from Questionnaire	Abeshouse (1956) 212 Cases Collected from Lit 1950–1955	Harvey (1950) 444 Cases Collected from Lit Prior to 1950	Creevy & Reiser (1951) 1170 Cases Collected from Lit	Scott (1954) 1141 Cases Collected from Lit.	Riches et al (1951) 189 Cases Collected in Great Britain Data on 138 Cases
1 Nephrectomy alone						
a No of cases	15	8	180		463	30
b Immed op deaths	0	0				
c Died in 1st yr	5	7				
d Survived 2 yrs	2 (13%)	1 (12 5%)	28* (15 5%)	52	87 (18 8%)	16 (53%)
e Survived 3 yrs						9 (43%)
f Survived 5 yrs	2	1 (12 5%)		34		6
g Survived 10 yrs	2			22		4
2 Nephrectomy plus post op irrad						
a Cases	250	128	109		347	61
b Immed mortality	5 (2%)					
c Died 1st yr	137 (54 8%)					
d Survived 2 yrs	38 (15 2%)	36 (28%)	33* (30%)	37	83 (23 9%)	20 (33%)
e Survived 3 yrs	21 (8 4%)	12 (9 3%)				10 (26%)
f Survived 5 yrs	23 (9 2%)	13 (10 1%)		13		6 (10%)
g Survived 10 yrs	9 (3 6%)	6		5		0
3 Pre op irrad nephrectomy post op irrad						
a Cases	128	45	65		132	14
b Immed op death	2 (1 5%)					
c Died 1st yr	64 (50%)					
d Survived 2 yrs	33 (25 8%)	14 (31 1%)	21* (32%)	23	42 (31 8%)	2 (14 2%)
e Survived 3 yrs	15 (11 7%)		3 (4 6%)			1 (7 1%)

* = 18 months survival

TABLE 4—*Continued*

	Abeshouse (1956) 434 Cases from Questionnaire	Abeshouse (1956) 212 Cases Collected from Lit. 1950–1955	Harvey (1950) 444 Cases Collected from Lit Prior to 1950	Creevy & Reiser (1951) 1170 Cases Collected from Lit.	Scott (1954) 1141 Cases Collected from Lit	Riches et al (1951) 169 Cases Collected in Great Britain Data on 133 Cases
f Survived 5 yrs	11 (8 2%)	7 (15 5%)		6		1
g Survived 10 yrs	6 (4 6%)	2		1		
4 Pre-op irrad nephrectomy						
a Cases	41	31	27		81	4
b Immed op deaths	0					
c Died 1st yr	18 (43 9%)					
d Survived 2 yrs	8 (19 5%)	3 (25 7%)	5* (18 5%)	16	21 (25 9%)	1 (25%)
e Survived 3 yrs						
f Survived 5 yrs	5 (12 2%)	5 (16 1%)		12		
g Survived 10 yrs	1	2		3		

exact significance is difficult to explain It is interesting to note that Harvey obtained almost similar results in a study of 444 cases collected from the literature prior to 1950

It is gratifying to note the increasing number of 5-year survivals in the series of 434 cases collected by the author from the questionnaire (41 cases) and in 212 cases collected from the literature between 1950 and 1956 (26 cases) These findings show a decided increase over the findings reported by Gahagan and Yearwood (1949) who collected only 35 cases of 5-year survivals in the literature of the previous 50 years It is also encouraging to note a higher percentage of 10-year survivals in the questionnaire and in the literature of the past 6 years

It was quite apparent that the results of the operative treatment were considerably influenced by the presence or absence of demonstrable metastases before or during operation Metastases were present in at least 412 cases treated by 41 authors

INFLUENCE OF AGE OF PATIENT UPON OPERATIVE RESULTS

A review of the literature and an analysis of the replies to the questionnaire indicate that the age of the patient should not be regarded as a contraindication to surgery in the absence of demonstrable local recurrence or general metastasis Silver, Deming and Campbell have successfully removed a Wilms' tumor from infants 3 days, 29 days and 42 days old, respectively

The studies of Gross and Neuhauser, Harvey and Scott reveal that the best

TABLE 5 *Effect of age on survival rate following operation*

Author	Cases Below 1 yr	Survivors Below 1 yr	Cases Above 1 yr	Survivors Above 1 yr	Cases All ages	Survivors All ages
Harvey 1950, collected cases	65	27 (41 5%)	407	75 (18 4%)	472	102 (21 6%)
Scott 1956						
A) Royal Child Hosp Glasgow	17	3 (17 6%)	46	3 (6 5%)	1068	111 (10 4%)
B) Collected series	161	28 (17 4%)	844	77 (9 1%)		
Gross & Neuhauser 1950						
A) 1914–1930		(42 8%)		(5%)	27	4 (14 9%)
B) 1931–1939		(71 4%)		(28 8%)	31	10 (32 2%)
C) 1940–1947		(80 0%)		(43 3%)	38	4 (47 3%)
Total					96	32 (33 3%)

results of the various operative methods are obtained when the condition is diagnosed and treated within the first year of life (table 5) Confirmation of this view is found in the replies of 93 surgeons who answered yes 51 times, no 20 times, 16 undecided and no opinion 7

TYPE OF OPERATIVE APPROACH

In recent years there has been a definite shift away from the use of the classical posterolateral lumbar incision in favor of the transperitoneal approach (table 6) This may be attributed in part to the refinements and improvements in operative techniques acquired during approved residency training in urology or pediatric surgery and in part to the introduction of better preoperative and postoperative management

In the transperitoneal approach, a longitudinal, transverse or T incision may be employed according to the preference and training of the surgeon Many surgeons utilizing this method of approach have repeatedly stressed the important technical consideration of exposing and ligating the renal vascular pedicle first in an effort to prevent dislodging and disseminating tumor cells during the process of freeing the tumor from the surrounding tissues These surgeons have maintained that the usual wide lumbar incision is inadequate for exposure of the renal pedicle and radical excision of any Wilms' tumor It should be emphasized that even in the transperitoneal approach, it may be impossible or extremely difficult to expose and ligate the vascular pedicle before mobilizing the kidney and tumor mass due to the unusual size, shape or position of the tumor

TABLE 6 *Type of operative approach preferred by 93 surgeons*

Operative Approach	Surgeons
1 Transperitoneal	50
2 Lumbar	24
3 Lumbar in average size tumors but in very large tumors	
a transperitoneal	15
b transthoracic	10
c Nagamatsu rib resection	4

In order to carry out a total removal of the kidney and tumor mass, the adjacent adipose tissue and the perirenal fascia, it is imperative to obtain an adequate and generous exposure. For those who prefer a lumbar approach, this may be greatly facilitated by utilizing the bone-muscle flap operation of Nagamatsu. For those who prefer the transperitoneal approach, difficult cases may be handled more easily by a combined thoraco-abdominal operation as advocated by Chute, O'Conor, and others.

THE ROLE OF IRRADIATION IN THE TREATMENT OF WILMS' TUMOR

There is considerable difference of opinion concerning the proper role of irradiation in the treatment of Wilms' tumors. In the past 20 years, several outstanding surgeons have presented reports of fairly large series of cases successfully treated by different plans of treatment which include some form of irradiation. In a study of 716 collected cases, Harvey was unable to establish striking statistical evidence to support any specific form of treatment involving surgery alone or combined with irradiation. It is now generally agreed that irradiation alone is unsuitable for the treatment of Wilms' tumor.

A brief discussion of the role of irradiation in the various plans of treatment with a statistical analysis of the replies to the questionnaire regarding irradiation alone or as a supplementary measure to nephrectomy is herewith presented.

PREOPERATIVE IRRADIATION

As has been noted previously, this form of therapy has been advocated by some and condemned by others. It should be strongly emphasized that this type of irradiation is not designed nor intended to be a curative procedure but serves as a valuable adjunct to surgical removal of the tumor mass. The extreme radiosensitivity of the tumor cells is well recognized and a rapid decrease in the size of the tumor can be expected. The amount of shrinkage in some cases is sufficient to make an inoperable tumor amenable to surgery. The main objection to this form of therapy has been the waiting period of 4 to 6 weeks advocated by Schenck, Rowe, and Fraser, and others, or the waiting period of 3 months advocated by Paterson. The recent experience of many competent radiologists attests to the feasibility and practicability of the administration of 1500–2000 r of irradiation or even larger doses in a period of 7 days followed by immediate surgery. While the amount of irradiation is governed by the response of the tumor, the time interval consumed need not exceed 7 to 10 days.

The amount and technique of preoperative irradiation have varied considerably in the past but in recent years there has been some effort to standardize this technique. The following technique has been utilized with some minor variations, viz.: 20 M.A. current, 200 K.V., target skin distance 50 cm., filtration through 0.5 mm. copper alone or combined with 1 mm. Al. The daily dose administered to one of several portals (an anterior and posterior field or one of 3 abdominal portals) usually falls between 100–200 r depending on the size of the tumor mass. In this manner, the total dose through each portal may be as high as 1500–2000 r which achieves a total dose of 3000 to 5000 r at the center of the tumor and in the region of the renal vascular pedicle.

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Total					96	32 (33.3%)

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By means of the questionnaire, the author has attempted to learn if preoperative irradiation was used as frequently today as in the past 20 years This type of therapy was employed by 52 authors, (i e , 34 routinely and 18 if tumor was very large) and not used by 41 Information concerning the duration of treatment was supplied by 40 surgeons, viz , 1–7 days by 4 surgeons, 2 weeks by 26 surgeons, 4 to 8 weeks by 6 surgeons and 3 to 4 months by 4 surgeons There has been a decided trend on the part of most surgeons to leave the dosage and duration of irradiation to the discretion of the radiologist

Do metastases occur during the period of preoperative irradiation? Gross and his co-workers strongly maintain that such is the case but base their opinion solely on clinical impressions, operative findings and survival rates Unfortunately there is no confirmation of this view by histological studies of the irradiated or non-irradiated tumor mass and adjacent tissue in large series of cases It is interesting to note that 52 surgeons believed that metastases could or did occur in the preoperative period of irradiation, 7 were contrary minded, 12 were undecided, and 12 failed to answer

Every one of 93 surgeons who answered the questionnaire agreed that preoperative irradiation produced a marked reduction in the size of the tumor Although there was no unanimity of opinion regarding the benefits of this therapy from the standpoint of increased operability and decreased technical difficulties, the consensus of opinion was for this modality as 74 indicated that a decided decrease in operative difficulties resulted and only 14 held an opposite view while 5 were undecided

In reply to the possible influence of variations of the histological patterns of Wilms' tumor upon the degree of response of tumor to irradiation, it was not surprising to find that 50 believed that the different histological types of tumors militated against a uniform response to irradiation, 21 held an opposite view, 12 were undecided and 10 gave no opinion

The contributors were asked to express a frank opinion of the general value of preoperative irradiation This type of therapy was regarded as beneficial by 52, a waste of time by 20 and undecided or no opinion by 21

POSTOPERATIVE IRRADIATION

This type of irradiation has gained fairly wide acceptance in the past 5 years as a result of the high 2-year survival rates reported by Gross and Neuhauser following immediate surgery and postoperative irradiation While the use of postoperative irradiation is less controversial than preoperative irradiation, some urologists question the advisability of this form of therapy Several aspects of this question merit further consideration

This author is of the opinion that justification for the employment of postoperative irradiation may be seriously questioned under the following circumstances 1) when the surgeon presumes that this form of therapy is curative, 2) the family is given the false impression that it is employed as a life saving procedure, 3) when this type of irradiation is regarded as a harmless form of therapy entirely devoid of after effects or complications, and 4) when the necessity of its use has not been clearly established by operative, clinical, pathological and roentgenographic studies

There are ample clinical and statistical studies to confirm the practicality of postoperative irradiation in combating local recurrences and distant metastases Yet one cannot ignore the impracticality of attempting to treat all possible metastatic sites which would require extensive radiation over almost the entire body surface in these small patients Experience has shown the necessity of exercising extreme caution in avoiding over-irradiation in these small patients with local recurrences or extensive metastases

The uncertain status of postoperative irradiation as a curative measure is borne out by the fact that only 26 of 93 surgeons believed that this form of therapy possessed any curative powers On the other hand, 70 of 93 surgeons did not hesitate to advocate irradiation as a palliative measure in the presence of demonstrable metastases or in inoperable cases

Undoubtedly many surgeons have intentionally or unintentionally employed postoperative irradiation as a prophylactic measure in cases of unproven local recurrences or distant metastases Small doses are ineffectual in killing live cells left behind and heavy doses sufficient to kill these cells are likely to kill the adjacent healthy cells with serious aftereffects On the other hand, one may question the absolute necessity of postoperative irradiation under the following conditions 1) when the tumor has been removed intact, 2) no evidence of local invasion can be demonstrated at operation, 3) no metastases can be demonstrated in the lungs or bones by roentgen studies, and 4) no evidence of arterial, lymphatic or retrograde venous spread or direct extension can be demonstrated on clinical and urographic examinations Under such circumstances, the surgeon may be satisfying his conscience and assuaging the wishes of the family by ordering postoperative irradiation under the false assumption that everything possible is being done to save the life of the patient

Several authors have reported startling results following irradiation of regional extensions and pulmonary metastases Nesbit and Adams successfully treated two cases by irradiation of regional infiltrations due to incomplete removal and a third case diagnosed by aspiration biopsy with pulmonary metastases was treated solely by irradiation with survival 10 years later Kerr reported a case of a 4-year-old girl treated by nephrectomy who subsequently developed pulmonary metastases which responded to irradiation and the patient was alive and well 52 months later

Dean has made a very practical suggestion to facilitate postoperative irradiation In those cases with actual or suspected extension of the tumor into the perirenal tissues he applied metallic clips in these tissues at the time of operation to sharply delineate the area to be irradiated postoperatively In this manner, the dangers of haphazard or needless extensive irradiation can be eliminated or minimized

Postoperative irradiation appears to have gained wide acceptance in this country and abroad The answers to the questionnaire indicated that this procedure was used routinely by 85 surgeons and was not used at all by 6 surgeons

Two surgeons employed this form of therapy only if the tumor was very large and metastases were encountered at operation or suspected It was the opinion of 61 surgeons that this form of therapy exerted a decided positive influence on the survival rate, an opposite view was held by 11 and no opinion was expressed by 21 This influence was manifested chiefly by the prevention of metastases in the opinion of 28 surgeons, whereas 25 maintained this therapy did not prevent metastases, 30 were undecided and 10 failed to answer

COMPLICATIONS AND SEQUELAE OF IRRADIATION

It must be acknowledged that irradiation therapy in the treatment of Wilms' tumor is not without its dangers, particularly in the postoperative phase which usually entails heavy radiation locally or at distant metastatic sites Although infants and children tolerate irradiation better than adults, varying degrees of constitutional reaction are manifested in all cases and a severe local reaction may occur in some cases

The following systems in the body are most frequently involved gastrointestinal, hematopoietic, osseous, pulmonary and renal

Gastrointestinal symptoms, i e , anorexia, nausea, vomiting, and diarrhea, are not uncommon sequelae and are usually mild and transitory In an occasional case distressing enteritis may occur The effect of heavy local irradiation on the hematopoietic system often is quite striking, i e , the bone marrow in the adjacent osseous structures may be severely damaged and anemia and leukopenia may ensue Barringer has reported fatal bleeding following irradiation

The most striking postirradiation changes are observed in the osseous system As a result of heavy local irradiation epiphyseal arrest may develop in the vertebra with resultant scoliosis Less frequently hypoplasia of the pelvic bones may occur which adds to the skeletal deformity Some surgeons have argued that such deformity is a small price to pay in an effort to cure a Wilms' tumor This skeletal defect may be avoided by employing smaller daily and total dosage over the local area Fortunately in many cases the skeletal deformity may be controlled or corrected by the utilization of proper orthopedic procedures

The more annoying complications of irradiation involve the lungs and kidney When heavy thoracic irradiation is employed in an effort to control pulmonary metastases, severe pneumonitis or pulmonary fibrosis may develop The latter lesions may be distressing during the period of irradiation but are not permanent in their effects and usually disappear after a varying period of time

Radiation nephritis is the most serious complication of irradiation Care and caution should be exercised in shielding the opposite healthy kidney when administering heavy local irradiation over the tumor area Unfortunately, the changes produced in the healthy kidney by indiscreet or careless irradiation are progressive and irreversible Campbell observed 3 cases of radiation nephritis with an early fatal outcome in 2 cases

It is rather surprising to note that the skin of infants and children is particularly resistant to roentgen rays No case of wound disruption following irradiation has been recorded in the literature or in the answers to the questionnaire

Complications of irradiation were reported by 26 surgeons The most common reaction was gastroenteritis which was of a mild nature in 9 cases and severe in 4 cases Radiation nephritis of the opposite kidney was reported in 8 cases and a delay in osseous development with skeletal deformity was observed in only 2 cases

The dosage and duration of postoperative irradiation revealed considerable variation This is to be expected as the use of this therapeutic measure in most instances is predicated on the presence or absence of local recurrence and distant metastases and consequently a uniform pattern and dosage are not always feasible Most urologic and pediatric surgeons relegated the responsibility for this therapy to the radiologist

The data on dosage and duration of postoperative irradiation are very meager The daily dosage varied from 90 to 200 r with an average of 150 r The total dosage varied from 2000 to 4000 r directed alternately through two portals (anteriorly and posteriorly over the tumor area) and occasionally a third portal (laterally) utilizing the same roentgen factors 200 K V , ½ mm copper filter at a target distance of 50 cm Some surgeons recommended postoperative irradiation every 6 to 8 weeks for at least 6 months after surgery even in the absence of demonstrable local recurrence or distant metastases

After reviewing the literature and analyzing the replies to the questionnaire, it is my opinion that a more rational approach to the use of irradiation in the treatment of Wilms' tumor is to treat each case as an individual therapeutic problem When the urological surgeon is confronted with a small, operable tumor no preoperative irradiation is required A very large tumor, which would render operation a difficult or formidable task, should be given preoperative irradiation in sufficient dosage to reduce the tumor to an operable size and the kidney removed promptly thereafter Intensive irradiation over the operative site or site of distant metastases should be reserved for the postoperative period This view is also held by Nesbit and Adams, Sauer, Creevy, Garrett and Mertz, and many others

PROGNOSIS

The outlook in cases of Wilms' tumor appears to be no different than in other malignancies where time and experience have repeatedly demonstrated that the earlier the diagnosis and treatment, the better the results It is unfortunate that the outstanding clinical signs and symptoms of Wilms' tumor are usually manifested or recognized too late in the course of the disease and by the time the patient is seen by the physician or surgeon, the tumor has attained large proportions and spread beyond the confines of the capsule rendering the condition inoperable or hopelessly advanced Priestley and Broders found the tumor to be inoperable at the time of initial examination in 37 of 65 cases, Millin maintained that between 40 to 60 per cent of cases were inoperable

Ladd Gross and others have maintained that no correlation exists between the size or histological structure of the tumor and results obtained by various methods of treatment Ladd and White were the first to point out that the prognosis is directly influenced by the age of the patient and showed that patients under one year have a decidedly better prognosis than those over one year This has been confirmed by the studies of Gross and Neuhauser, Harvey, Scott and Creevy (see table 5)

There is an apparent need for a *more accurate interpretation of results* On the basis that most recurrences following surgery occur within a period of 18 months, Ladd, and later Gross, have regarded survival beyond the time period as a "cure" While this may be true in some cases, there have been frequent reports of recurrences and deaths from metastases 2 to 20 years following surgery Consequently it would appear more logical and more accurate to regard those living 18 months after surgery as "survivals" rather than "cures"

One of the most debatable and thought-provoking aspects of the entire problem of Wilms' tumors is the determination of who is best qualified to carry out the treatment of this condition Much has been said but little has been written to determine the advantage of delegating this responsibility either to the urological surgeon or the pediatric surgeon Consequently this perplexing situation has led to bitter contention and animosity between these two classes of surgeons and to confusion and indecision on the part of the pediatrician, general practitioner, internist, and others Recently in some large university affiliated hospitals or in highly specialized clinics or hospitals devoted to the care of children, the responsibility for the diagnosis and treatment of this condition has been divided between the pediatrician, urologist, pediatric surgeon and the radiologist In such institutions, the services of the urologist are utilized for establishing or confirming the diagnosis by appropriate cystoscopic or urographic procedures but the operation is usually performed by the pediatric surgeon However in most non-university affiliated hospitals and some affiliated hospitals, where the overwhelming majority of cases are treated, the responsibility for the diagnosis and care of the patient usually falls on the physician (pediatrician or general practitioner) who first sees the patient This physician promptly obtains the services of a urologist who establishes the diagnosis and performs the operation

This urologist is usually board-certified or at least board-qualified, has spent four to five years acquiring a well rounded urological training and a variable number of years in urological practice where he obtains an extensive experience in handling all types of surgical and non-surgical diseases of the kidney in adults and children including renal neoplasms and a wide experience with the various pediatric urologic problems By virtue of his training and practice, the urologist is more likely to have a greater familiarity with the different problems arising in the diagnosis, differential diagnosis, pathology, treatment and preoperative and postoperative care of Wilms' tumors than the pediatric surgeon whose experience is usually limited to the operative aspects of renal disease in children It would seem that in the vast majority of cases occurring in the average urban hospital the interests of the patient are best served by the combined efforts of the pediatrician, the urologist and the radiologist with the responsibility for the surgical treatment placed on the urologist It should be hardly necessary to point out that in this age of surgical specialization the operative treatment of this serious condition should never be entrusted to a "general" surgeon whose experience with renal diseases is decidedly meager

CONCLUSIONS

The following conclusions are based on a detailed analysis of the replies of 93 surgeons to a comprehensive questionnaire, an extensive review of the literature and a personal experience with 6 cases of Wilms' tumor.

Wilms' tumor of the kidney is the most common tumor of the urinary tract in infancy and childhood.

These tumors occur with equal frequency in each sex and each kidney. There is a higher incidence of bilateral tumors than previously suspected as the author has collected a total of 44 cases. The tumor is most frequently encountered in the first four years of life and in this series of 856 cases the average age was 3.2 years.

The classical triad of symptoms of renal tumor, i.e., hematuria, pain and tumor mass, is present simultaneously in a very small percentage of cases. The incidence of these symptoms is reversed in cases of Wilms' tumors, viz., tumor mass 85 per cent, pain 30 per cent and hematuria 10 per cent.

The consensus of opinion is that operation can be safely postponed until an accurate diagnosis is established. An overwhelming majority recommend a combination of two or three diagnostic methods (i.e., palpation, excretory urography and retrograde pyelography) with a decided preference for all three modalities.

A diagnosis based solely on palpation was employed only by a few surgeons and is a practice to be condemned, for it may lead to an incorrect diagnosis, an unnecessary operation, needless sacrifice of conservable renal tissue and an increased operative mortality and morbidity. On the other hand, rough and frequent palpation should not be permitted.

An analysis of the methods of treatment employed by the surgeons answering the questionnaire indicated the following choice in order of frequency: 1) nephrectomy plus postoperative irradiation (44 per cent), 2) preoperative irradiation plus nephrectomy and postoperative irradiation (22 per cent), 3) preoperative irradiation plus nephrectomy (10.2 per cent), and 4) nephrectomy alone (5.2 per cent). Irradiation alone was never the procedure of choice being employed in only inoperable or bilateral cases (7.2 per cent).

An accurate statistical comparison of the different methods of treatment is difficult or impossible because of several unknown and many variable factors indicated elsewhere.

A study of the results of treatment in 777 operative cases revealed several striking findings, i.e., a very low operative mortality 2.7 per cent, a very high percentage of patients dying in the first postoperative year (54.3 per cent) and a relatively low number of patients surviving two or more years. These results are encouraging but far from satisfactory particularly in respect to the high number dying in the first year and the low survival rate of 2 years or more.

A detailed study was made of 434 cases submitted by 52 surgeons and revealed that better results were obtained by preoperative irradiation plus nephrectomy and postoperative irradiation than by nephrectomy and postoperative irradiation, i.e., lower mortality rate (1.5 per cent 2 per cent), decrease in deaths in first postoperative year (50 per cent 54.8 per cent), and an increase in 2-year survivals (25.8 per cent 15.2 per cent).

A study of 212 cases reported in the literature between 1950 and 1955 also showed a slightly higher 2-year survival rate in those treated by preoperative irradiation, nephrectomy and postoperative irradiation than those treated by nephrectomy and postoperative irradiation (31 1 per cent 28 per cent)

The results of operative treatment are definitely influenced by the presence or absence of local extension and distant metastases as determined prior to or during operation

The best results are obtained when the condition is diagnosed and treated during the first year of life

The transperitoneal approach is more desirable than the classical postero-lumbar retroperitoneal approach from the standpoint of operability and results In the case of a very large tumor, removal of the tumor may be facilitated by employing bone-muscle flap technique of Nagamatsu or the thoraco-abdominal approach

The role of irradiation as a supplementary measure to surgery in the treatment of Wilms' tumors is still a highly controversial subject Inasmuch as Wilms' tumor and its local extensions and metastases are extremely radio-sensitive, it is important that preoperative and postoperative irradiation should not be regarded as separate modalities having different effects and used for different purposes

The advantages claimed for preoperative irradiation include 1) marked reduction in the size of the tumor rendering the operation easier and safer in the moderate sized tumor and feasible in large or so-called inoperable tumors, 2) the irradiation changes within the tumor decrease the likelihood of blood loss, tumor spread and metastases, and rupture during the operation, 3) during the period of irradiation, the general condition of the patient may be improved by the use of transfusions, antibiotics and intravenous fluids and 4) for many urological surgeons this method has yielded a reduced operative mortality and an increased survival rate

The chief objection to preoperative irradiation has been the waiting period of 4 weeks to 3 months which may easily be overcome by the administration of 1500–2000 r or even larger doses in a period of 7 to 10 days followed by immediate surgery

Postoperative irradiation has gained wide acceptance among urologists in the past 5 years as a result of the high 2-year survival rates reported by Gross The feasibility of this type of irradiation in combating local recurrence and distant metastases cannot be denied The indiscriminate use of this type of irradiation as a prophylactic measure in cases of unproven local extension or recurrence or distant metastases is open to question

It should be emphasized that irradiation as an adjunct to surgery is not without its dangers particularly when heavy doses are administered locally or at distant metastatic sites Post-radiation changes may involve the gastrointestinal, hematopoietic, osseous, pulmonary and renal systems The most serious complication is radiation nephritis whose changes are usually irreversible and not infrequently fatal

A rational approach to the use of irradiation in the treatment of Wilms' tumor is to treat each case as an individual problem, i e , a) small, operable tumors require little or no irradiation, b) large tumors should receive sufficient dosage within a very short period to reduce the tumor to operable size and the kidney promptly removed, c) intensive radiation over operative area or the site of distant metastases should be reserved for the postoperative period in proven cases of local extension or recurrence and/or metastases

In the past, the prognosis in cases of Wilms' tumor has been poor but has been improved in the past 10 years as a result of improvement in operative technique and better pre- and postoperative management Surgery combined with irradiation has yielded ever increasingly better results from the standpoint of operative mortality, morbidity and survival rate and has done much to dispel the feeling of helplessness and hopelessness

The urologist is better qualified by virtue of his training and experience to assume the responsibility for the diagnosis and operative treatment of Wilms' tumors

Closer co-operation between the pediatrician, the urologist and the radiologist in the future will undoubtedly lead to much better results

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CASE REPORT

A Mexican woman, 43 years of age and married, came to the outpatient department of the Santa Clara County Hospital on September 21, 1954. She complained of pain in her right flank.

The day before her clinic visit she had noted the sudden onset of dull, constant, right flank pain radiating to her right inguinal region and right anterior thigh. This had persisted with some slight dysuria and frequency. She had had no hematuria, nausea or fever. She described a similar episode which had occurred 1 year previously. This had lasted 1 day and subsided without treatment.

The patient gave no history of trauma, passage of calculi, or urinary infection during her six normal pregnancies. Her systemic review was negative.

The patient's temperature was 98F, the pulse rate 78, and the blood pressure 90 mm. systolic and 60 diastolic. Significant findings included a soft abdomen with no masses or tenderness. The liver and spleen were not palpable. She had no costovertebral angle tenderness nor audible bruit over the right renal area. The lower pole of the right kidney was palpable and non-tender.

Urinalysis revealed a urinary pH of 6.5 with a specific gravity of 1.011. Tests for albumin and sugar were both negative. Microscopic examination revealed 1–3 white blood cells per high dry field. No red blood cells were found. The concentration of hemoglobin was 11.5 gm. per 100 cc. of blood. Erythrocytes numbered 3,500,000 and leukocytes 8,900 with a normal differential count. The blood serologic reaction (VDRL) was negative and the urea nitrogen content 10 mg. per 100 ml. Roentgenograms of the chest were normal. Intravenous urograms revealed a pressure defect compressing the upper, lower calyx with inferior displacement of the lowermost calyx of the right kidney (fig. 1, A). No intrarenal calcification was seen.

Retrograde pyelography confirmed the intravenous urographic findings.

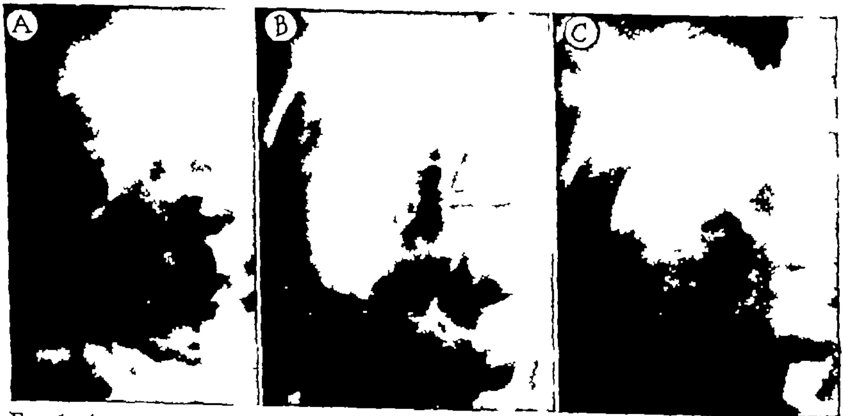

FIG. 1. A, intravenous urogram shows compression of upper lower calyx with displacement of lowermost calyx. B, translumbar aortogram (arterial phase) showing outline of intrarenal aneurysm. C, translumbar aortogram (nephrogram) showing prompt emptying of aneurysm.

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INTRARENAL ANEURYSM OF THE RENAL ARTERY CASE REPORT

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Aneurysm of the renal artery is rare It has been found to occur in one of 8,200 autopsies[1] and one of 13,525 autopsies [2] Abeshouse[3] in 1951, in his review of the 115 cases reported to that date, could find only 10 originating from the intrarenal vessels

From a pathologic standpoint, renal artery aneurysms are divided into two types 1) true, 2) false True aneurysms are those in which the wall of the localized vascular dilatation is composed of the vessel wall itself, which has been weakened by some demonstrable pathologic process such as arteriosclerosis, or else are congenital in origin False aneurysms are the result of traumatic rupture of the vessel wall with the formation of a perivascular hematoma Organization of this hematoma forms a vascular space which communicates with the original vascular lumen through the traumatic perforation Therefore, the wall of a false aneurysm is composed of hyalinized fibrin derived from the organized hematoma

Symptomatically, the patient may no have difficulty until the aneurysm ruptures, or intermittent flank pain, a palpable mass or hematuria may occur Physical examination may reveal hypertension, a palpable flank mass, abnormal abdominal pulsation, bruits or murmurs over the area

Laboratory findings are usually normal Radiographic examination of the abdomen will often reveal a wreath-like, calcified ring in the region of the renal vessels This can be localized by means of oblique films, intravenous, or retrograde pyelography Dos Santos[4] in 1930 was the first to recommend the use of arteriography as an aid in the diagnosis of renal aneurysms It has recently been advocated by several authors—Reagan et al ,[5] Burns et al [6] and Begner [7]

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lining Elastic stain delineated a well-defined internal elastic lamina Both trichrome and Van Gieson stains showed numerous smooth muscle fibers persisting in the wall of the aneurysm The kidney was otherwise not remarkable

DISCUSSION

Since all vascular layers were present in its wall this was by definition, a true aneurysm Because the remaining vascular system appeared normal, this may represent a congenital aneurysm developing at a vascular bifurcation as described by Forbus[5] From his study of congenital aneurysms of the cerebral mesenteric and coronary arteries he concluded that there exists at the bifurcation of vessels a weakness due to a naturally occurring deficiency of the smooth muscle fibers of the muscularis at this point In addition, his studies indicated that there was probably an initiating degeneration of the internal elastic lamina These defects, combined with the elevated hydrostatic pressure normally found at an arterial bifurcation resulted in a ballooning of the central wall at that point of weakness Since no other cause could be found the intrarenal aneurysm reported here may be of congenital origin

SUMMARY

A report is made of a patient with intrarenal aneurysm The aneurysm was demonstrated conclusively by translumbar aortography and confirmed by surgical extirpation Since no other evidence of vascular disease was found, this was assumed to be of congenital origin

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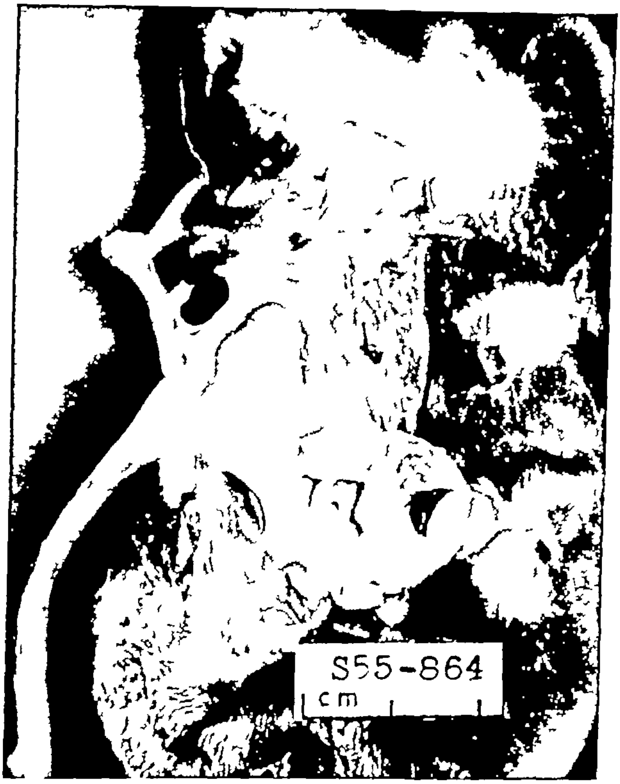

FIG 2 Cross section of right kidney shows aneurysmal sac at lower pole

A translumbar aortogram resulted in immediate filling of a sac-like dilatation of a branch of the renal artery to the lower pole of the right kidney (fig 1, *B*) This dilated segment of the vessel measured 2 5 cm in diameter and had a smooth margin An immediate followup film showed complete emptying (fig 1, *C*)

A diagnosis of probable intrarenal aneurysm was made and a right nephrectomy was performed through an eleventh rib incision Palpation of the kidney revealed no gross abnormality

Pathologic examination revealed a grossly normal appearing right kidney measuring 11 6 by 5 0 by 4 1 cm The capsule stripped with ease revealing a smooth, reddish-brown surface An anomalous branch of the right renal artery extended to the lower pole of the kidney When the kidney was halved, a 2 5 cm cystic appearing space having a vascular wall was encountered at the juncture of the lower and middle calyces (fig 2) This cystic structure was empty Its wall was composed of a grayish-white, fibrous tissue about 0 1 cm in thickness The luminal surface was only slightly roughened Although this lesion was in close association with the lower branches of the renal artery, no efferent vessel could be demonstrated

Microscopic examination revealed the wall of the cystoid structure to be composed, for the most part, of dense laminated connective tissue with an endothelial

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PLASTIC OPERATIONS UPON THE URETER WITHOUT INTUBATION

E A WEBB, B A SMITH, JR AND W E PRICE

Over a short period of observation it has become apparent to us that plastic operations on the ureter without intubation, as described by Drs Frank Hamm and Sydney Weinberg, simplify the technique of these operations and produce results that are uniformly satisfactory

This report deals with observations made upon eighteen plastic operations done on the ureter without intubation Eleven of these operations were done for relief of obstruction at the ureteropelvic junction one for relief of obstruction due to retrocaval ureter, and six were made to reimplant the ureter into the bladder

The data show that the period of hospitalization is shorter and that the immediate followup results are good Additional apparent advantages are conservation of renal tissue by eliminating the trauma of nephrostomy, fewer febrile reactions, less likelihood of calculus formation and ureteral stricture because of elimination of tubes, particularly plastic catheters in respect to the latter complication The operative procedure is shorter, healing is more rapid as evidenced by the quick disappearance of pyuria, and the patients seem to be more comfortable

Postoperative urinary drainage from the wound has not proved to be a disadvantage of this procedure Possible disadvantages are fistula formation and stricture at the site of plastic repair because of elimination of the splinting catheter

Considering the one case of retrocaval ureter in the category of non-calculous obstruction at the ureteropelvic junction, there were 12 cases of hydronephrosis of this etiology Eight of these were due to anomalous vessel obstruction and four were classified as stricture at or near the ureteropelvic junction The circumstances requiring reimplantation of the ureter into the bladder were trauma in 4 cases and neoplasm in 2 cases

The type of pelvioureteroplasty used to relieve the obstruction at the ureteropelvic junction varied In this particular series one conventional Foley Y-plasty and eleven ureteroneopelviostomies were performed Five of the latter were dismembered Foley Y-plasties and six were excisions of the ureteropelvic junction with elliptical anastomosis of the ureter to the pelvis The only variation from the accepted and established procedure of pelvioureteroplasty was the utilization of the suggestions recommended by Drs Hamm and Weinberg These recommendations were that the procedure be performed without using a splinting catheter, without nephrostomy, and by providing drainage with a Penrose drain down to a small stab wound in the posterior wall of the renal pelvis In most instances nephropexy was done by suturing the posterior renal capsule of the lower pole of the kidney to the quadratus lumborum muscle

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Read at annual meeting, North Central Section of American Urological Association, Cleveland, Ohio, October 3-5 1956 vein Artery and vein were divided close to the aorta Ureter and kidney were removed The postoperative course was uneventful

The gross pathological specimen showed very little distortion of the kidney proper There was a dilated, tortuous renal artery The specimen, divided with a probe passing from artery to vein, showed a large intrarenal aneurysm between the two (fig 2)

The patient has done well postoperatively and has had no further cardiac signs or symptoms His heart shadow on chest x-ray, which preoperatively was markedly distended, has now returned to within normal limits His preoperative nonprotein nitrogen was 34 mg per cent, rose to 52 mg per cent immediately after operation and is now 31 mg per cent His serum creatinine was 0 6 mg per cent, rose to 1 9 mg per cent postoperatively and is now 0 8 mg per cent

A complete review of the literature on this subject was recently reported by Doctors Slominski-Laws, Kiefer and Vermeulen in the JOURNAL OF UROLOGY (vol 75, pp 586–591, 1956) the right flank for 2 years The attacks were severe at times and lasted for as long as 5 days His appendix was removed during one of these attacks without relief The patient's urine was normal

The excretory urogram showed right hydronephrosis and a normal left kidney The retrograde urogram showed hydronephrosis with a large renal pelvis and angulation of the ureteropelvic junction probably due to anomalous vessels

At operation the renal pelvis was found to be remarkably dilated and the kidney was judged to show 50 per cent atrophy There were two large accessory vessels and fibrous adhesions anterior to the region of the junction which applied the ureter to the pelvis The major portion of the renal pelvis was excised and a dismembered Foley Y-plasty was done with the anastomosis anterior to the vessels A stab wound was made in the posterior surface of the pelvis above the anastomosis

There was urinary drainage from the wound for the first 48 hours but none thereafter The patient was discharged from the hospital on the ninth postoperative day

An excretory urogram, made 3 months postoperatively, showed good function of the right kidney, no hydronephrosis and some irregularity of the inferior medial margin of the pelvis which was probably the result of operative deformity

Case 3 C K was a man aged 36 Ten days before the patient presented himself for examination he had had gross hematuria with questionably mild discomfort occurring in the right flank 24 hours prior to the symptom of hematuria There was a past history of the right ureteral colic occurring 16 years previously No calculus was recovered

The excretory urogram showed the left kidney and ureter to be normal Right hydronephrosis was present No filling of the right ureter occurred

The retrograde urogram revealed the ureter to be of normal caliber except that it was a bit dilated below the true junction and there was application of the ureter to the pelvis with a high position of the junction

At operation there was an anomalous vessel crossing the ureteropelvic junction anteriorly This very likely was the cause of the obstruction but the relationship could not be definitely established because the pelvis had been deflated prior to dissecting out the junction A dismembered Foley Y-plasty was done with a stab wound in the posterior wall of the pelvis There was urinary drainage from the wound for 8 postoperative days but none thereafter The patient was discharged from the hospital on the ninth postoperative day

An excretory urogram made 3 months postoperatively, revealed prompt appearance of the dye in the right kidney The concentration of the dye is a bit less on the right The patient's urine is normal

Case 4 E McG , a girl aged 20, gave a history of several episodes of right flank pain occurring over a period of one year

The excretory urogram revealed an anatomical set-up for obstruction at the ureteropelvic junction but only minimal hydronephrosis No dye was noted in the right ureter

The retrograde urogram made during an attack of mild pain revealed definite

Ureteroneocystostomy was performed by suturing the full thickness of the ureter to the full thickness of the vesical wall In some instances, the full thickness of the ureter was sutured to the vesical mucosa and then reinforcing sutures were placed from the vesical musculature to the ureteral adventitia One ureteroneocystostomy was done using a tubular vesical graft to bridge the defect between the distal end of the ureter and the bladder No splinting catheters were used in the procedure of ureteroneocystostomy Tissue drainage was accomplished by Penrose drains

The following observations were made Any drainage from the wound requiring reinforcement or a change of the primary dressing during the first 24 hours following operation was considered indicative of urinary drainage The longest period of postoperative urinary drainage following pelvioureteroplasty was 8 days In several instances there was no postoperative urinary drainage at all The average period of postoperative urinary drainage following pelvioureteroplasty was 3 5 days The average period of postoperative urinary drainage following ureteroneocystostomy was 6 8 days Likewise some of these patients had no postoperative urinary drainage, whereas one patient had urinary drainage for 17 days The average period of hospitalization following pelvioureteroplasty was 7 6 days, whereas formerly the minimum was 14 days The average period of hospitalization following ureteroneocystostomy was 11 6 days

A few case summaries will be presented to illustrate the points made in the foregoing discussion

CASE REPORTS

Case 1 J H , a girl aged 4½ years, during a 2-month period experienced two episodes of left flank pain with chills, fever and pyuria The excretory urogram revealed the left renal outline to be enlarged with no filling of the collecting system The right kidney and ureter were normal Retrograde urography demonstrated left hydronephrosis with obstruction at the ureteropelvic junction At operation the obstruction was found to be due to anomalous vessels These vessels supplied the lower half of the kidney The kidney was judged to be two thirds normal size The renal pelvis was transected on an oblique line running from the lateral margin upward and medially just proximal to the ureteropelvic junction and sutured together again anterior to the vessels Two elliptical surfaces were thus presented for closure of the pelvis The caliber of the ureteropelvic junction was normal A stab wound was made in the posterior wall of the pelvis above the line of closure

No leakage of urine from the wound occurred postoperatively The patient was discharged from the hospital on the eighth postoperative day The urine was normal 15 days after the operation

A postoperative excretory urogram, made 3 months after the operation, showed prompt appearance of dye in the left kidney and ureter There was no hydronephrosis There have been no episodes of left acute pyelonephritis The urine is normal

Case 2 R G , a man aged 22, had experienced intermittent episodes of pain in postoperative urinary drainage has not been a problem The use of the stab wound in the renal pelvis can probably be eliminated without altering the results

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hydronephrosis with considerable retention of dye in the pelvis 10 minutes after the dye was injected

The obstruction was due to stricture and a Foley Y-plasty was done without splints and with a stab wound in the posterior pelvic wall

Urine drained from the wound 8 days following the operation The patient was discharged from the hospital on the eighth postoperative day The urinary drainage, which had been very slight for several days, ceased the day the patient left the hospital

An excretory urogram, made 3 months postoperatively, revealed the right kidney to be normal The patient has had no further attacks of pain

Case 5 A S, a woman aged 40, complained of intermittent attacks of right renal pain

Excretory urogram and retrograde urogram showed right hydronephrosis and medial displacement of the upper ureter The preoperative diagnosis of the right retrocaval ureter was confirmed at operation

Repair was made by obliquely excising a portion of the renal pelvis, drawing the ureter and lower pelvis from behind the vena cava and reanastomosing the edges of the renal pelvis without using a splint A stab wound for drainage was left in the pelvis

Urine drained from the wound 3 days, otherwise the postoperative course was uneventful

Nine months later the urine was clear Excretory urograms showed good drainage and marked reduction in the size of the right hydronephrotic sac

Case 6 L McA, a woman aged 49, underwent an abdominal hysterectomy for uterine fibromyomas A right ureterovaginal fistula developed 6 weeks later

The excretory urogram showed right hydronephrosis and a normal left kidney Right ureteroneocystostomy was performed by suturing the ureteral wall to the vesical mucosa and placing a few supporting sutures from the vesical wall to the ureteral adventitia No splinting catheter was used A urethral Foley catheter was left indwelling in the urinary bladder for 7 days Uneventful recovery without urinary leakage occurred Urinalysis was negative and the excretory urogram was normal 7 months postoperatively

Case 7 R H, a woman aged 53, had two vesicovaginal fistulas and a right ureterovaginal fistula that followed a Wertheim operation for cervical carcinoma Three months later a tubular bladder flap reconstruction of the right lower ureter was necessary due to extensive fibrosis No splint was used The vesicovaginal fistulas were closed A retrograde cystogram showed right vesicoureteral reflux Excretory urogram, 4 months later, revealed the upper urinary tract to be normal

SUMMARY AND CONCLUSIONS

Eighteen patients with successful plastic operations on the ureter without the use of splinting catheters have been presented These operations included 12 pelvioureteroplasties and six ureteroneocystostomies Short hospitalization periods and good immediate postoperative results have been shown Excessive

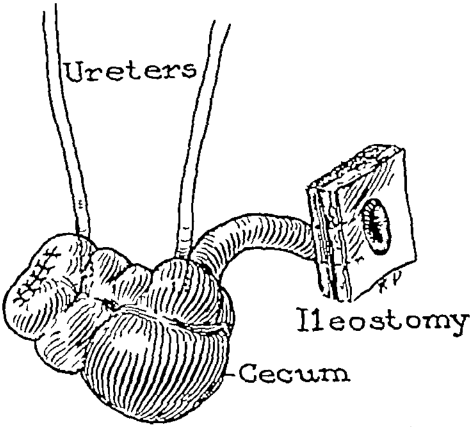

FIG 1 Artificial bladder, constructed with portions of cecum and ileum

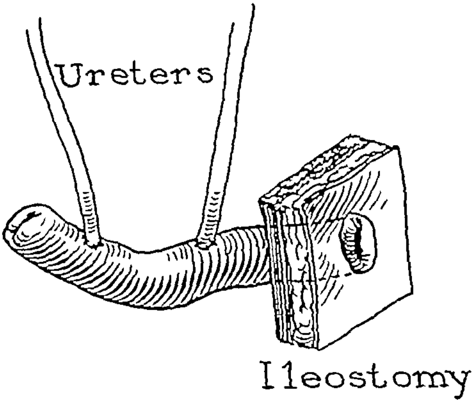

FIG 2 Artificial bladder in which ileum is utilized

In Pyrah's[2] excellent paper on ureterocolic anastomosis, he mentioned a case in which he successfully bridged a gap between a short upper segment of ureter and the bladder, with the use of an isolated segment of ileum The thought occurred to me that it might be possible to use a segment of ileum to enlarge the urinary bladder in instances of contracted bladder If a side-to-side anastomosis was used to join the segment of ileum to the dome of the bladder, a normal ureterovesical juncture and a normal vesical neck could be maintained, with the distinct possibility of normal vesical function I performed two such operations, they will be described next

REPORT OF CASES

Case 1 —A 53-year-old white woman first registered at the Mayo Clinic on July 6, 1950 She complained chiefly of constant suprapubic pain and frequency of urination, both of which had been present for 3 years Moreover, the symptoms had gradually become severer, in spite of treatment The first effort to

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[2] Pyrah, L N Uretero colic anastomosis Ann Roy Coll Surg England, 14 169-197, 1954

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ENLARGEMENT OF THE URINARY BLADDER WITH A SEGMENT OF ILEUM

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When the urinary bladder contracts to such a degree that its capacity is reduced to 30 or 40 cc, it ceases to function, and the unfortunate patient is distressed by the constant dribbling of urine Moreover, the upper part of the urinary tract is affected adversely because dilatation takes place, and as this complication progresses, renal function becomes impaired One of the commonest causes of this contraction is interstitial cystitis

In the past, in an attempt to relieve this distressing and serious situation, diversion of the flow of urine has been accomplished by the performance of bilateral nephrostomy, cutaneous ureterostomy and ureterosigmoidostomy All these methods have had disadvantages When the first two were carried out, there followed the inconvenience to the patient of the draining of urine to the outside and the necessity of employing a collecting receptacle Infection invariably developed which was a constant, chronic process, superimposed on it were episodes of acute pyelonephritis These complications gradually but surely produced renal insufficiency When ureterosigmoidostomy was done the use of an external receptacle was not necessary, but infection was always a threat Another disadvantage, which sometimes was serious, was the change in the electrolyte pattern of the blood [1]

Because of these disadvantages, other means of diverting urine were sought Consideration was given to the construction of an artificial bladder This procedure involved the use of one of three different isolated segments of bowel, namely, the cecum and ileum, a coil of ileum, and the rectum and sigmoid (figs 1, 2 and 3) I have used the cecum and ileum in the following manner The cecum and 4 inches of ileum are isolated, care being taken to preserve the blood supply The cecum is closed, both ureters are anastomosed to it, and the ileum is brought out in the form of a structure which could be called a ' urethra " Intestinal continuity is established by performance of ileo-ascending colostomy In two-thirds of the cases it was found that the ileocecal valve was competent and that the patient needed intermittent catheterization two or three times a day In the remaining third, the use of an indwelling catheter was necessary In my cases, infection has been absent, except for an occasional episode of acute infection, and the electrolyte balance of the blood has not been disturbed

A coil of ileum has been used by others in a similar manner, but when that particular technique is used urine, of course, drains to the outside and requires the use of some external apparatus When the rectum and sigmoid were utilized in a somewhat similar procedure the anal sphincter was employed to control the exit of urine, but the operation left the patient with a colonic stoma

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Read at the meeting of the North Central Section of the American Urological Association, Cleveland, Ohio, October 3-5, 1956

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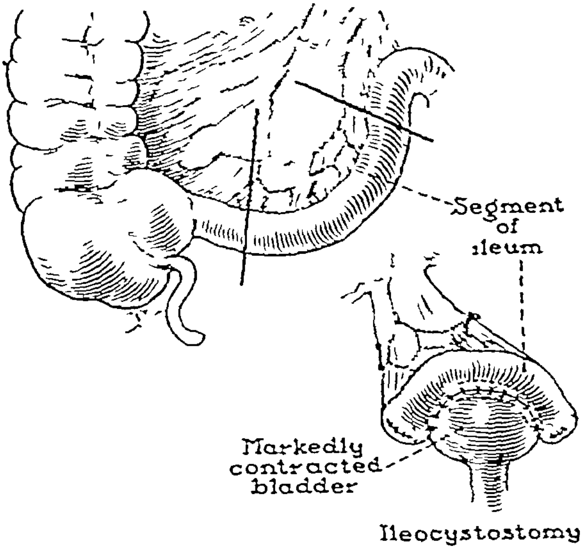

FIG 4 Ileocystostomy in which an 18 cm segment of ileum was employed in case 1

Operation was performed on July 13, 1954, through a secondary low midline incision Exploration of the abdomen revealed the abdominal organs to be normal The uterus and appendix had been removed A segment of ileum 18 cm in length was isolated and intestinal continuity was re-established by ileoileostomy, with the use of end-to-end anastomosis The ends of the isolated segment were closed and an incision was made in the antimesenteric border, extending almost to the end The dome of the bladder was then incised transversely and a side-to-side anastomosis was used to attach the isolated segment of ileum to the bladder (fig 4) A urethral catheter was placed in the bladder

The patient's postoperative course was uneventful On the fourteenth day after operation the urethral catheter was removed, the patient voided without difficulty and emptied the bladder completely Three weeks after the operation cystoscopy was carried out The vesical wall was seen to be unchanged the suture line was well healed and the capacity of the bladder was approximately 300 cc The patient voided without pain and at intervals of 3½ to 4 hours She was dismissed on August 11, 1954, and was advised to take sulfacetimide (sulamyd) the first week of each month to rest the second week to take aureomycin the third week and to rest the remaining days of the month She returned to her teaching position and remained perfectly comfortable

On December 28, 1954, the patient was re-examined, she was found to be free of symptoms and the urinary tract was normal Pyuria, however, persisted, but it had abated much A retrograde cystogram (fig 5) disclosed normal vesical capacity

The patient reported by letter in March 1955, that she was entirely normal At the time of this report she had been entirely normal for more than 2 years

After a year's test, I was satisfied that the operation was a success, at least

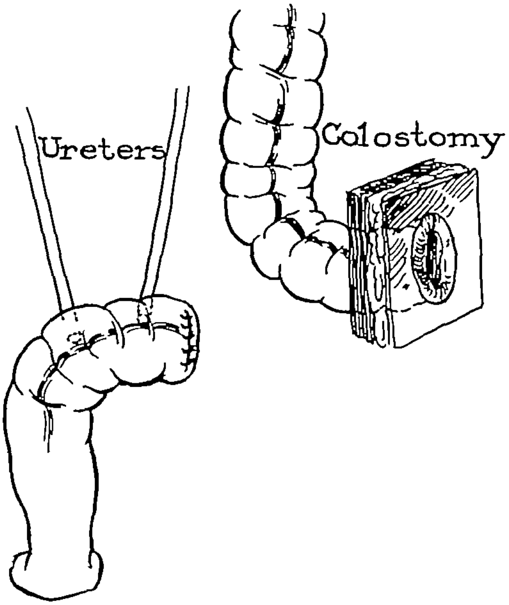

FIG 3 Artificial bladder constructed with portions of sigmoid and rectum

alleviate the symptoms had been surgical, and consisted of abdominal hysterectomy, supposedly performed to relieve pressure on the bladder The second measure consisted of the instillation of a solution of silver nitrate into the bladder, this had been done on several occasions

The patient was healthy, except for the urinary tract The upper portion of the urinary tract was normal Urinalysis revealed pyuria, and cystoscopic examination showed typical interstitial cystitis to be present Treatment at this time consisted of overdistention of the bladder with the patient under the influence of anesthesia, subsequently, increasing strengths of a solution of silver nitrate were instilled into the bladder daily She improved greatly and continued treatment under supervision of her local physician

On July 1, 1954, the patient returned to the clinic because vesical symptoms had become most severe Suprapubic pain was constant and severe, and frequency of urination had progressed to the point of dribbling incontinence Her condition had caused her to give up her position as a schoolteacher

Our observations were much the same as those of the previous examination, except that the interstitial cystitis was much worse and the inflammation had caused much scarring, fixation and contraction of the bladder Vesical capacity was reduced to 50 cc After careful deliberation and consultation, my colleagues and I advised the patient to consider an attempt to enlarge vesical capacity by the attachment of a segment of ileum to the bladder This proposal was accepted, and the patient was admitted to the hospital and prepared for operation, meaning that a low-residue diet was prescribed for 2 days, the bowel was cleansed by means of enemas, phosphate of soda (Fleet's phospho-soda) was administered orally and terramycin was given

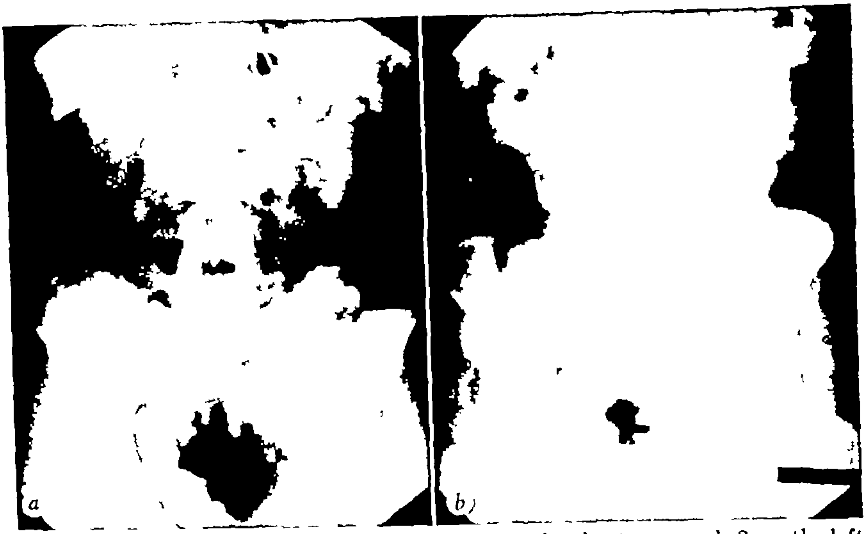

FIG 6 *a* Preoperative excretory urogram showing pyelocaliectasis grade 2, on the left in case 2 *b* Excretory urogram, made 6 months after operation in case 2 shows pyelocaliectasis, grade 3, with fairly good function remaining

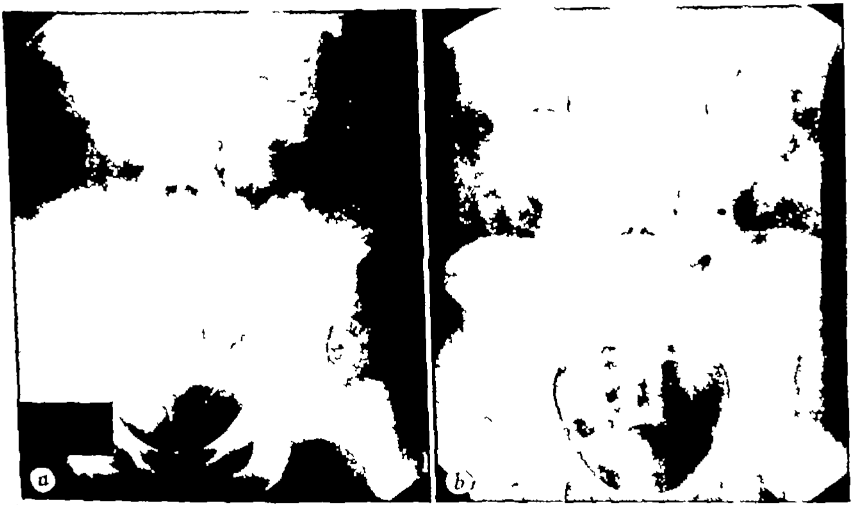

FIG 7 *a*, Retrograde pyelograms made 6 months after operation in case 2 Note progression of pyelocaliectasis on left, to grade 3 *b*, Upper part of urinary tract is normal, as shown in this excretory urogram made 4 months after meatotomy and 11 months after ileocystoplasty in case 2

ectasis, grade 2 (fig 6*a*), developed on this side At this point we advised the patient to consider enlargement of the bladder by means of a segment of ileum He accepted the suggestion The preoperative preparation and surgical procedure were the same as in case 1

The patient's postoperative course was uneventful The catheter was removed on the fourteenth day after the operation, the patient voided without difficulty

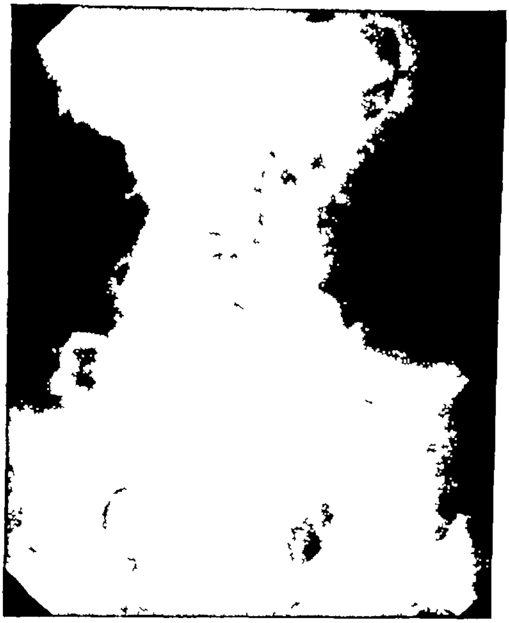

FIG 5 Retrograde cystogram which shows normal vesical capacity postoperatively in case 1

in the female I did not know whether or not the operation would be successful in males, but within a month a man presented himself who, it seemed, might be benefited by the procedure

Case 2 —A 34-year-old white man had first registered at the Mayo Clinic on August 11, 1947 He complained chiefly of extreme urgency and frequency of urination

He was healthy, except for the urinary tract The upper portion of the urinary tract was normal Urinalysis revealed pyuria and cystoscopic examination showed congenital contracture of the vesical neck The vesical neck was dilated to the size of a 26F catheter, after which the pyuria cleared rapidly The patient was advised that transurethral prostatic resection might be indicated if symptoms recurred They did recur, and the patient was almost constantly under the care of a physician at home, where he underwent transurethral resection of the prostate gland and, later, excision of the urachus

The patient returned to the clinic on February 7, 1954, because frequency and urgency of urination had persisted The upper part of the urinary tract was normal, but cystoscopic examination disclosed subacute cystitis Several specimens of tissue were removed for study, and proved to be inflammatory The bladder was irrigated with silver nitrate for 3 weeks, at the end of which time the symptoms had about disappeared Yet cystoscopic examination demonstrated interstitial cystitis

During the next 18 months the picture was that of interstitial cystitis, with gradual lessening of vesical capacity until the bladder would hold only 50 cc The inflammation was most marked in the left half of the bladder, pyelocali-

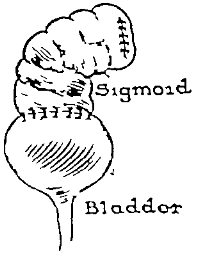

Fig 8 Method of increasing capacity of urinary bladder by utilizing sigmoid colon in cystoplasty

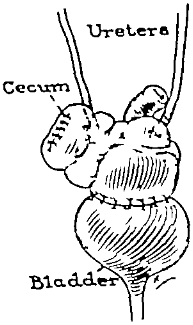

Fig 9 Method of increasing capacity of urinary bladder by utilizing part of cecum and ascending colon in cystoplasty

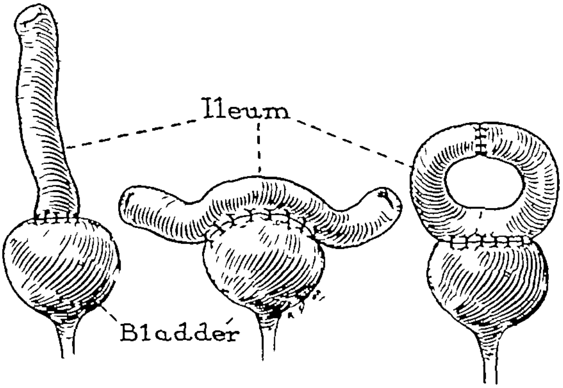

Fig 10 Three different ways in which ileum can be used to increase capacity of urinary bladder (Left) one end of ileum is closed, and other is anastomosed to bladder, (center) both ends of ileum are closed and center is anastomosed to bladder, (right) anastomosis of center of ileal loop to bladder, open ends being joined to form continuous ring

Although in most of the cases described the enlarged bladders functioned fairly well, there were both anatomic and physiologic difficulties The earliest difficulty described was prolapse of the intestinal segment into the bladder It was in an effort to correct this condition that Scheele developed his ring technique A second difficulty was poor emptying of the bladder, in many instances this was caused by a small stoma That is, in the presence of a small stoma the segment of bowel functioned much like a vesical diverticulum with a small neck Most of the surgeons have attributed the emptying of the segment of and emptied the bladder completely The vesical capacity was 400 to 425 cc, urgency and frequency of urination had completely disappeared The patient was dismissed 4 weeks after the operation

Six months later the patient returned because of an increasing ache in the left flank He had no vesical symptoms, however Excretory urograms and retrograde pyelograms revealed pyelocaliectasis, grade 3, on the left (fig 6*b* and 7*a*) Cystoscopic examination showed that the ileal patch looked very much like normal vesical tissue However, some degree of inflammation remained in the region of the left ureteral orifice Left ureteral meatotomy was done, 4 days later the patient was allowed to return to his home

On June 13, 1956, 4 months after the meatotomy and 11 months after the ileocystoplasty, the upper part of the urinary tract of this patient was normal (fig 7*b*) and the bladder was functioning normally

COMMENT AND CONCLUSION

Pyrah[2] referred to the excellent work of Couvelaire,[3] reported in 1950 I have found this work most interesting Apparently, tuberculosis is much more prevalent among the French than among Americans, and Couvelaire has done much work on the contracted bladder in association with this disease He reviewed the literature from 1898, when Mikulicz made the first attempt to enlarge the bladder with the use of an isolated segment of bowel, to 1950 During this time the European literature was augmented by a number of reports of single cases in which some isolated part of the intestine had been anastomosed to the bladder Sometimes an isolated segment of sigmoid colon was used (fig 8), sometimes a short segment of ascending colon and cecum (fig 9) was employed, but probably more frequently an isolated segment of ileum was used This segment of ileum was utilized in three different ways (fig 10) In some cases one end of the isolated segment was anastomosed to the bladder and the other end was closed (fig 10, left), in others, the center of the segment was anastomosed to the bladder and both ends were closed (fig 10, center) Scheele[4] in 1941 reported the anastomosis of the center of an isolated segment of ileum to the bladder, the ends of the loop were joined, thereby producing a continuous ring of ileum anastomosed to the bladder (fig 10, right) Scheele was able to collect 20 such cases from the literature, in 10 of these the operation had been done according to his own technique Couvelaire[3] described 5 cases of his own In 3 cases he utilized the cecum and in two the ileum Two of the patients in whom the cecum had been used died in the early postoperative period The third patient did poorly because the anastomosis was too small But the two patients in whom the ileum was used did very well

In 1953 Cibert[5] reported that he had performed ileocystoplasty for 17 patients One of these operations had been done more than 2 years previously, and the result was very satisfactory in every way

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VARIOUS PRACTICAL USES OF THE CONDOM FOR MANAGEMENT OF THE NEUROGENIC BLADDER

A ESTIN COMARR

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This paper presents 1) a practical method to retain catheters without a Foley bag, or to use a catheter whose Foley bag has been broken for two-way irrigation of the bladder, and 2) simple methods of preparing a condom as an attachment for the use of "external drainage" in the management of neurogenic bladders without a catheter

The use of a Foley bag catheter for the treatment of "imbalanced neurogenic bladders"[1] has become a routine procedure Obviously, it has many advantages over the bias-tape and/or tape halters used to retain catheters[2, 3] However, in my experience, Foley bags have frequently initiated acute exacerbations of chronic cystitis with gross bleeding, or caused multiple inflammatory polypoid vegetations around the ureteral orifices

Many Foley catheters are being discarded because of dehiscence of the bags either from the effect of repeated sterilization, or from induced rupture of the bag within the bladder when the bag could not otherwise be emptied Such catheters were salvaged and used for two-way irrigation by attaching the condom catheter retainer (fig 1) The condom is fixed to the penile skin with "facing cement," which is commonly used for the attachment of colostomy bags Should this not suffice, then it is re-enforced by a strip of elastoplast which is applied around the entire circumference of the penis Still another method of fixation has been recently suggested[4] which uses two plastic band-aids between the inside of the condom and the penile skin

The advantages of the condom catheter retainer are as follows A) It does not interfere with erections, B) it collects urine which is ejected around the catheters by a spastic bladder and, thus, prevents soiling of bedding and clothes, C) it can also be used where irrigation of the urethra at the penoscrotal junction or elsewhere is desired, this is achieved by merely adding holes into the inlet and/or outlet channels at the level of pathology[5], D) it permits salvage of discarded Foley bag catheters for the use as 1) a two-way catheter to irrigate the bladder by instilling through the former bag inlet the appropriate therapeutic solution (fig 2), and 2) as a straight drainage catheter by sealing off that inlet (fig 3)

Accepted for publication July 16, 1956

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bowel to intestinal peristalsis The formation of mucus in the lumen of the bowel occasionally has been troublesome

Because we know that absorption is the main function of the lower portion of the ileum, we might expect physiologic difficulties to be serious when a segment of the ileum is used in the manner described In the laboratory Bollman and Mann[6] showed that transplantation of the ureters into the *intact* small intestine usually leads to rapid death of the animal Davids and Bellwin,[7] however, have shown that in dogs, if an *isolated* segment of ileum longer than 20 cm is filled with urine, disturbances of electrolytes in the blood will ensue, but such disturbances will not take place if the segment used is shorter than 20 cm Couvelaire,[3] working with human beings, found that an isolated segment of ileum 25 cm long or less could contain urine constantly and yet not cause disturbance of the electrolytes of the blood

The cases reported herein involve not so much anastomosis of the ileum to the bladder as they do plastic enlargement of the bladder in which a segment of ileum is used as a sheet of material, rather than as a tube Being much more pliable than the thickened, contracted vesical wall, the portion of ileum behaves as an accordion pleat During filling of the bladder the portion of ileum is pushed out, and during micturition a slight increase in intra-abdominal pressure pushes it in, as a pleat would be pushed in The enlarged bladder empties completely There is no lumen in which mucus can collect and prolapse does not occur, as such The ileal segment is small Disturbance of the electrolytes of the blood has not ensued

I therefore conclude that the use of a short segment of the lower part of the ileum is suitable anatomically and physiologically for plastic enlargement of the urinary bladder in either sex

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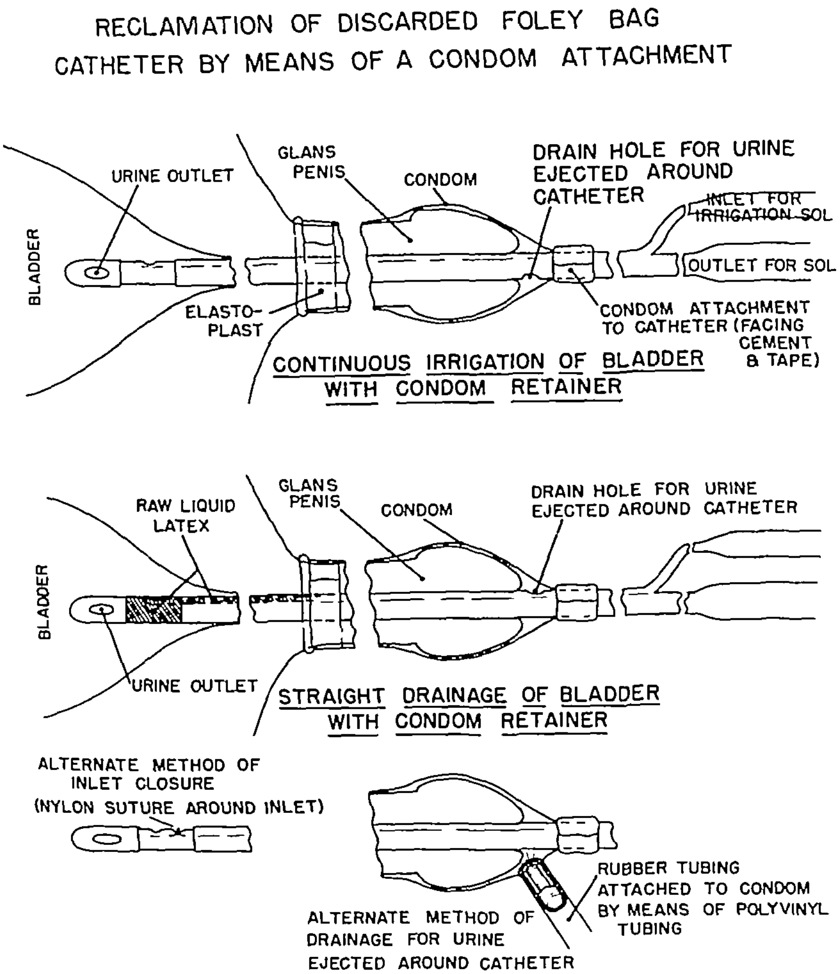
RECLAMATION OF DISCARDED FOLEY BAG CATHETER BY MEANS OF A CONDOM ATTACHMENT
BLADDER
URINE OUTLET
GLANS PENIS
CONDOM
DRAIN HOLE FOR URINE EJECTED AROUND CATHETER
~~INLET FOR IRRIGATION SOL~~
OUTLET FOR SOL
ELASTO-PLAST
CONDOM ATTACHMENT TO CATHETER (FACING CEMENT & TAPE)
CONTINUOUS IRRIGATION OF BLADDER WITH CONDOM RETAINER
BLADDER
RAW LIQUID LATEX
GLANS PENIS
CONDOM
DRAIN HOLE FOR URINE EJECTED AROUND CATHETER
URINE OUTLET
STRAIGHT DRAINAGE OF BLADDER WITH CONDOM RETAINER
ALTERNATE METHOD OF INLET CLOSURE (NYLON SUTURE AROUND INLET)
RUBBER TUBING ATTACHED TO CONDOM BY MEANS OF POLYVINYL TUBING
ALTERNATE METHOD OF DRAINAGE FOR URINE EJECTED AROUND CATHETER

Fig 3 Methods of preparing discarded Foley bag dependent on whether it is to be used for continuous two way irrigation or straight drainage of bladder Retainer of catheter with all modifications is condom

The modified discarded Foley bag catheters are diagrammatically shown in figure 3 The various methods of draining the urine accumulated in the condom because of ejection of urine around the catheter are noted The diagrams also show the methods of preventing urine from draining out of the inlet channel when the discarded Foley bag catheter is to be used only for straight drainage, namely, filling the inlet channel with raw liquid latex or sewing a nylon suture around the channel If the urine is not ejected around the catheter used for straight drainage only, one may simply close the inlet channel by folding the entrance of the inlet channel with a rubber band

The condom method of retaining the discarded Foley bag catheters functions well in bed However, when in a wheel chair the stretch of the condom may pull the catheter tip out of the vesical neck Therefore, if the patient is to be per-

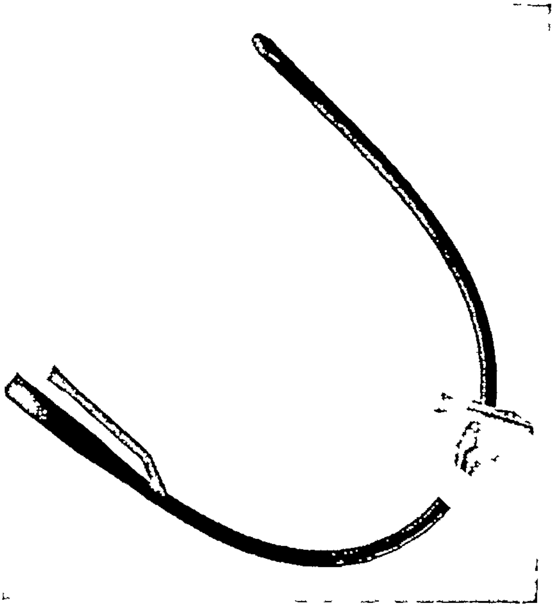

FIG 1 Foley bag catheter with condom attached by means of "facing cement" and tape Note that remnants of "broken bag" have been entirely removed Internal meatal opening for bag acts as inlet for continuous irrigation of bladder

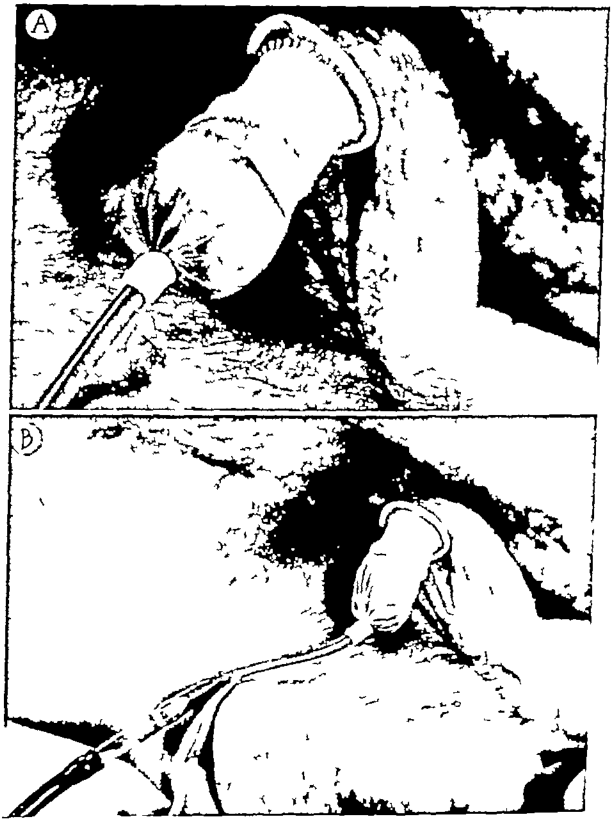

FIG 2 A, condom filled with urine ejected around catheter B, urine ejected around catheter has passed through hole into outlet channel of salvaged Foley bag catheter which is being used in this patient as a two way continuous flow irrigator

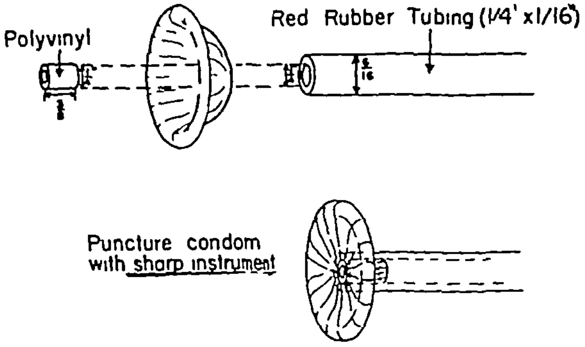
Polyvinyl
Red Rubber Tubing (1/4' x1/16')
1/16
Puncture condom with sharp instrument

Fig 6

mitted in a wheel chair the bias-tape or rubber strip halter is used to retain the discarded Foley bag catheter (fig 4) Obviously, this latter method is not satisfactory in a spastic bladder which ejects urine around the catheter The rubber strips keep the halter much cleaner than the cotton bias tape

It should be noted that ureteral catheters can also be held in position with or without an accompanying intraurethral catheter

It is my impression that many bladders may probably fare better without a Foley bag, despite the fact that many bladders tolerate it well Moreover, there are patients who develop penile excoriations, irrespective of the type of attachment to the skin Therefore, a compromise is now possible to alternate the use of non-Foley bag and Foley bag catheters as indicated by the status of the bladder

Paull presented a condom coupled urinal apparatus in 1953[6] Yet, when visiting other institutions in our area in which paraplegics are treated, one still finds patients with balanced neurogenic bladders who retain their catheters for want of something better Paull's aforementioned apparatus requires the preparing or purchasing of a plastic (lucite) adaptor in order to connect the condom and tubing This adaptor is then re-used each time when the condom is changed Figure 5 shows a simpler method of constructing the apparatus by the exclusive utilization of tubing and condom This gadget has been in use at this center for many years Figure 6 shows a still more recent innovation which is practical Both of our condom drainage apparatus have the advantage of being discarded after use without the problem of disconnecting and salvaging an adaptor

SUMMARY

A condom retainer for catheters has been described It can be used to retain any type of intraurethral catheter, although it was originally designed to salvage discarded Foley bag catheters for use as two-way catheters in the neurogenic bladder, it lends itself also for application in the wide field of general urology

Two simple methods of making condom drainage apparatus are presented with the plea to use them for the management of neurogenic bladders with a well balanced function

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[6] Paull, D P A condom coupled urinal for incontinence J Urol , 69 462, 1953

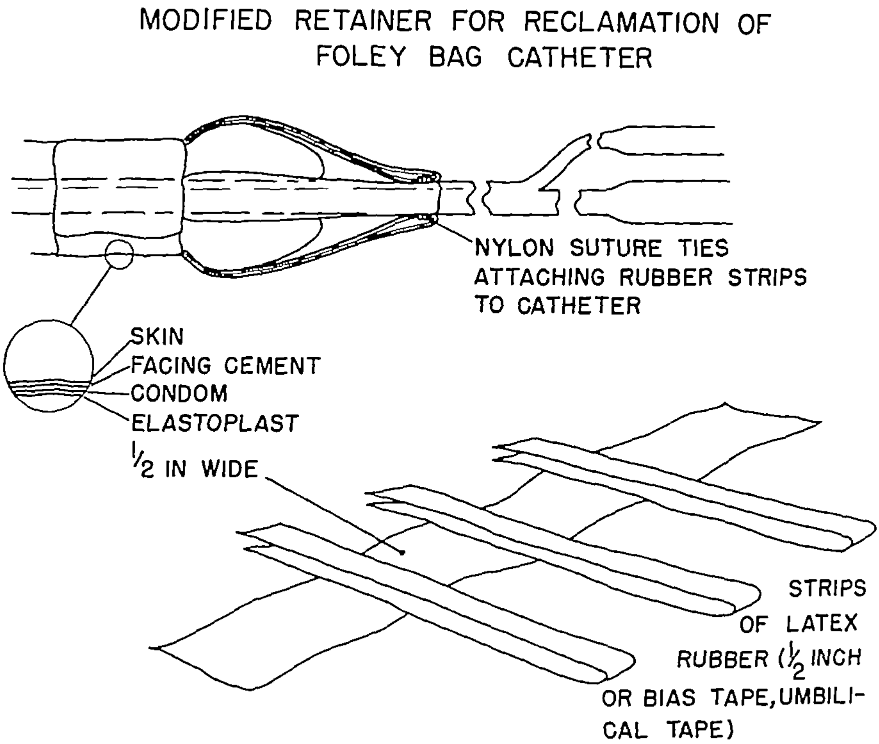
MODIFIED RETAINER FOR RECLAMATION OF FOLEY BAG CATHETER
NYLON SUTURE TIES ATTACHING RUBBER STRIPS TO CATHETER
SKIN
FACING CEMENT
CONDOM
ELASTOPLAST
1/2 IN WIDE
STRIPS OF LATEX RUBBER (1/2 INCH OR BIAS TAPE, UMBILICAL TAPE)

FIG 4 Retainer of discarded Foley bag is halter which has been used for many years This retains catheter more securely for wheel chair patient Rubber strips are more sanitary than cotton bias tape

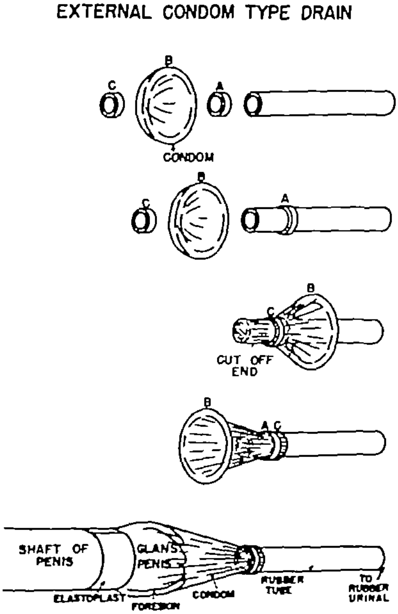

FIG 5

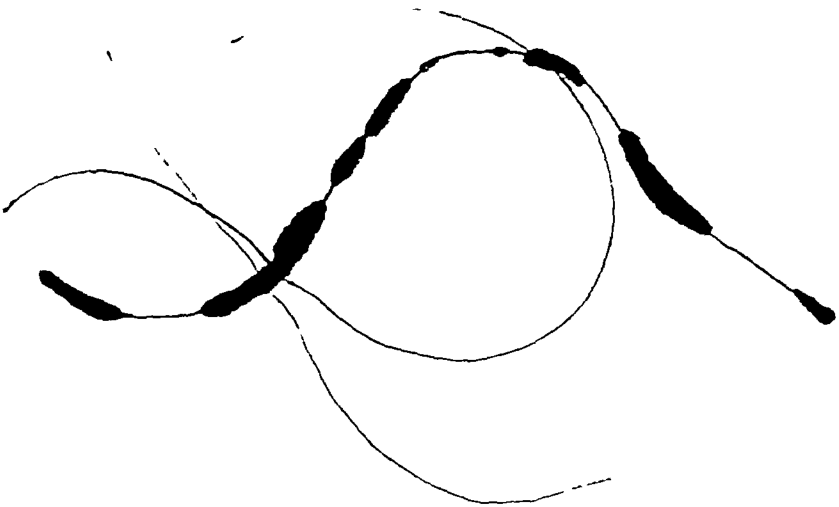

FIG 1 Case 2 Transilluminated photograph magnified four times illustrating representative hair strands Early calcareous deposits on one of hair strands are seen

cervical vertebra and a complete spinal lesion developed at the sixth cervical level The patient was maintained on internal urethral catheter drainage In January 1954 the patient underwent litholapaxy for multiple bladder calculi, and in February 1954 a transurethral resection of the bladder neck was performed Because of a high residual urine, he was continued on internal urethral catheter drainage In July 1955, a routine x-ray film revealed recurrent bladder calculi necessitating a second litholapaxy Following this procedure the patient continued on internal urethral catheter drainage with weekly changes On August 13 1956 another x-ray film revealed questionable, small calcifications in the urinary bladder On August 16 1956 cystoscopy was performed Examination revealed multiple strands of free hair floating in the bladder Multiple, small calculi had already begun to form around some of these hair strands The foreign material (fig 1) was easily removed from the bladder by means of an Ellik evacuator The patient's postoperative course was uneventful

Case 3 W D No 423 373 a 20-year-old white, paraplegic man was injured in a diving accident in May 1956 He had been on indwelling urethral catheter drainage since that time The patient was admitted to the Veterans Administration Hospital Hines, Illinois on August 17, 1956, and underwent initial routine urological examination An intravenous pyelogram on August 20 showed normal upper urinary tracts bilaterally with no evidence of calculi Cystoscopy was performed August 30, 1956, and multiple, flattened calculi were found to be present in the bladder These calculi were of such size that litholapaxy was necessary During the examination, multiple hair strands were found to be entwined around one of the larger calculi Unfortunately, the calculus had to be crushed in order to remove it by endoscopic means, and the specimen could not be preserved for photography

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HAIR AS A LOWER URINARY TRACT FOREIGN BODY

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Because the presence of free hair in the urinary bladder or the urethra is rarely encountered, the occurrence of six such instances is considered to be of interest A multitude of foreign objects have been described and summarized by Campbell, Dakin, and Brewer and Marcus, however, no instances of free hair in the urinary bladder have been reported Powell has removed a cat's hair from the ureteral orifice of a 4½-month-old girl French states that pilimiction is a rare manifestation indicating a rupture of a dermoid cyst into the bladder

Free hair suspended in the distending media was observed on six separate occasions during routine urethroscopic and cystoscopic examinations on the Paraplegic Section of the Veterans Administration Hospital, Hines, Illinois Small calculi had begun to form about the hair strands (fig 1) in two of these cases, and in a third case, free hair was found to be entwined about a larger bladder calculus All of these patients were paraplegics with indwelling urethral catheters Each one denied masturbation or the insertion of any object into the urethra, and there was no history of a penetrating bladder injury No characteristic symptoms were associated, but an x-ray revealed the presence of bladder calcifications in two of these cases The diagnosis in all 6 cases was made on panendoscopic examination Simple irrigations sufficed to remove the foreign material from the bladder in all cases except one, in which litholapaxy was required The most probable etiological factor appears to be the introduction of hair into the bladder during catheter changes, a secondary factor being the progression of hair along the urethral catheter during the frequent erections experienced by some of the paraplegic patients

ILLUSTRATIVE CASES

Case 1 J M, No 380 180, a 30-year-old white, paraplegic man was injured July 1954 in an automobile accident that resulted in a spinal lesion at the sixth cervical level Since that time, the patient had been maintained on an indwelling urethral catheter On April 8, 1955, the patient underwent litholapaxy for multiple, soft, bladder calculi He remained on indwelling urethral catheter drainage following this procedure His urethral catheter was changed at weekly intervals Repeated flat films of the abdomen demonstrated no change until May 4, 1956, when calcifications in the bladder area were noted Six days later, cystoscopic examination revealed a collection of hair in the bladder Multiple, rounded calculi were forming, using the hair as a nidus An Ellik evacuator removed the foreign material from the bladder, and the patient's postoperative course was uneventful

Case 2 G F, No 422 932, a 27-year-old white, paraplegic man was injured in July 1953, while diving into shallow water He sustained a fracture of the sixth

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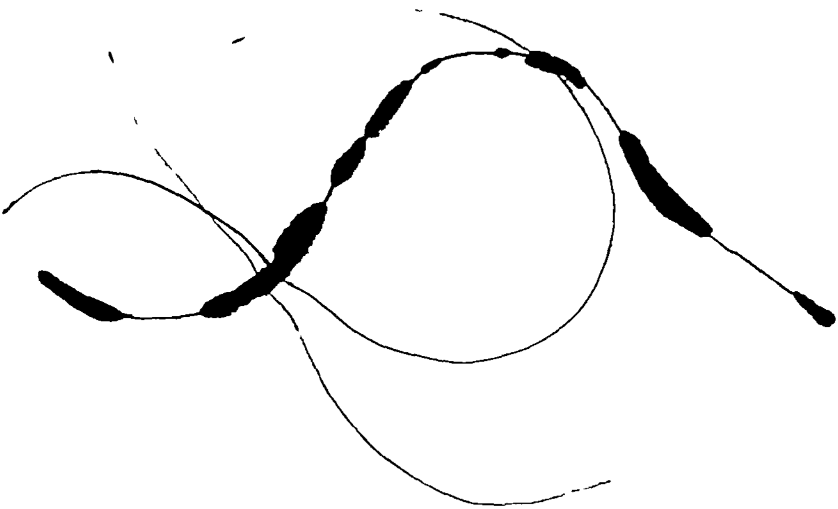

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Case 4 G V , No 391 511, a 30-year-old Mexican paraplegic man was injured by a gunshot wound in 1950, resulting in a physiological lesion at the third lumbar level Since that time indwelling catheter drainage had been used Also in 1950, a diagnosis of pulmonary tuberculosis was made, and the patient received antituberculous therapy Intravenous pyelograms were within normal limits on routine visits On August 31, 1956, the patient underwent routine urological examination During urethroscopy, a ball of hair matted around inspissated pus was found to be present in the bulbous portion of the urethra This was pushed back into the bladder with the beak of the panendoscope Further examination of the bladder revealed no evidence of calculi The bladder findings were essentially negative except for chronic cystitis With the aid of the Ellik evacuator, the entire mass of hair was removed from the bladder with relative ease

DISCUSSION

Five instances of free hair in the urinary bladder and one of free hair in the urethra were diagnosed by endoscopic examination It is a matter of conjecture in the sixth case whether the hair found in the urethra was pulled down into the urethra from the bladder when the indwelling catheter was removed just prior to cystoscopy, or whether the hair found in the urethra had been ascending along the catheter In two of these cases, multiple calculi had formed, using the hair as a nidus, in a third case, hair had wound itself around a larger calculus This report illustrates the meticulous care necessary in cases requiring periodic catheter changes Not only hair, but other foreign objects may be introduced into the bladder if poor catheter technique is practiced An infection of the bladder ensues, followed by calculus formation, ultimately leading to an involvement of the upper urinary tract Such a complication can be prevented by a) education of the supervising physician, his designated assistants, or the patient as to proper catheter technique, b) reducing self-catheterization to a minimum, c) cutting or shaving the genital hair in those cases requiring prolonged catheter drainage, d) periodic urological survey

SUMMARY

Five cases of free hair in the urinary bladder and 1 case of free hair in the urethra were observed on endoscopic examination

Hair had been a nidus for calculus formation in 2 cases, hair had entwined itself about a calculus in a third case

The importance of meticulous catheter technique is emphasized to prevent free hair from being introduced into the bladder during a catheter change

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1005 W Belmont Ave , Chicago 13, Ill

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TOTAL URETHRECTOMY FOR CARCINOMA OF THE FEMALE URETHRA

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Carcinoma of the female urethra is not a rare disease Although only 328 cases could be found in the literature in 1950 [1] others since have added 25 cases in one report [2] 10 in another [1] etc The author has seen 5 female patients with carcinoma of the urethra and there can be no doubt that the incidence of this disease is greater than the number of reported cases would indicate The incidence as related to female hospital admissions varies greatly At the Mayo Clinic 1 in approximately 233 000 female admissions was found [3] In Canada 1 in approximately 1 200 was reported [4] At Milwaukee County Hospital a ratio of 1 in less than 16,000 female admissions occurred over a seven-year period

The fact that this disease is not more common detracts in no way from its severity and the almost uniformly poor prognosis Fricke and McMillan[5] report a 10-year survival rate of 33 per cent Counseller and Paterson[6] find the same percentage of 5-year survivals Ruch[7] a 5-year cure rate of 37 per cent, and Flocks[8] 36 per cent apparent cures Counseller and Paterson[6] state that the average length of life is 16 months after the diagnosis is made

That the prognosis of this disease is poor is further emphasized by the wide variety of therapeutic procedures that have been advocated Prior to the 1920 s the emphasis was predominantly upon local surgical excision In the pre-radium era O Conor[9] called attention to the value of electrocoagulation and later electroresection was added With the development of irradiation therapy Counseller and Paterson[6] concluded that radium and x-ray in combination offered the best hope Fricke and McMillan[5] recommended local excision followed by radium Currently in the furor of extremely radical cancer surgery there are advocates

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Read in part at annual meeting North Central Section of American Urological Association Cleveland Ohio October 3-5 1956

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Ritter D W Primary malignancy of the female urethra West J Surg Obst & Gynec 61 420–429 1953

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of total cystourethrectomy with transplantation of the ureters[10] and even radical pelvic exenteration In short, almost all methods and combinations of cancer therapy have been used, and none has been entirely satisfactory Among the few patients who have been cured, the method of treatment has been as varied as it has been in the failures

The controversy over treatment is further complicated by differences of opinion as to the best management of the lymph nodes The primary lymphatic drainage of the female urethra is to the inguinal and femoral nodes bilaterally and also directly to the deep pelvic nodes Dean[11] states that metastases frequently are present when the tumor is first recognized and believes that if inguinal nodes are involved the pelvic nodes probably are also

Concerning the management of the lymphatics a majority advocate the Basset type of surgical excision Others favor various types of irradiation or a combination of irradiation and surgery Some prefer to withhold radical lymph node dissection until metastases are apparent [12] [13]

The purpose of this paper is to recall an overlooked surgical procedure which can be performed with ease, is relatively innocuous to the patient, and is of value in selected cases in the treatment of this serious disease

The first total urethrectomy with suprapubic drainage for carcinoma of the female urethra was performed by McGill[14] in 1890 During the turn of the century others[15–19] reported isolated cases, and gynecologists were considering the procedure for inoperable vesicovaginal fistulas In the early 1930's Counseller and Paterson[6] reported 2 cases, one a 1-year and the other a 2-year cure Black[1] added two more, one a 5-year and one a 6-year cure Ritter[9] then reported a 2-year cure and another dead in 20 months of unrelated causes but with no evidence of recurrence Roth[20] added a 20-month's cure in 1955

In a comprehensive review of the literature the author could find but 14 cases of total urethrectomy with suprapubic drainage for carcinoma of the female urethra Of the 14 one was palliative although described as satisfactory 7 months later Ten of the remaining 13 cases gave followup reports, and all of these 10 reported cures ranging from 9 months (1 case) to 6 years On the basis of these cases plus the case to be presented it would seem that total urethrectomy is of value in select cases of carcinoma of the female urethra

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[10] Riches, E W and Cullen, T H Carcinoma of the urethra Brit J Urol , 23 209–221, 1951

[11] Dean, A L Carcinoma of the male and female urethra Pathology and diagnosis J Urol , 75 505–513, 1956

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[20] Roth A A Carcinoma of the female urethra Ohio State Med J , 51 872–874, 1955

A question might be raised about the possibility of unrecognized bladder tumors developing in the bladder which has been closed from below Dean[11] emphasises that primary tumors of the urethra are rarely associated with tumors of the bladder In addition, as in the case to be presented, cystoscopy can be performed periodically with relative ease through the cystostomy site

REPORT OF CASE

Mrs L S, age 53, was hospitalized for the care of edema and ulcerations of her lower extremities Thirty-two years previously she had had multiple pelvic operations followed by peritonitis and thrombosis of deep pelvic vessels Since then she had been hospitalized repeatedly for edema of both lower extremities with stasis ulcerations

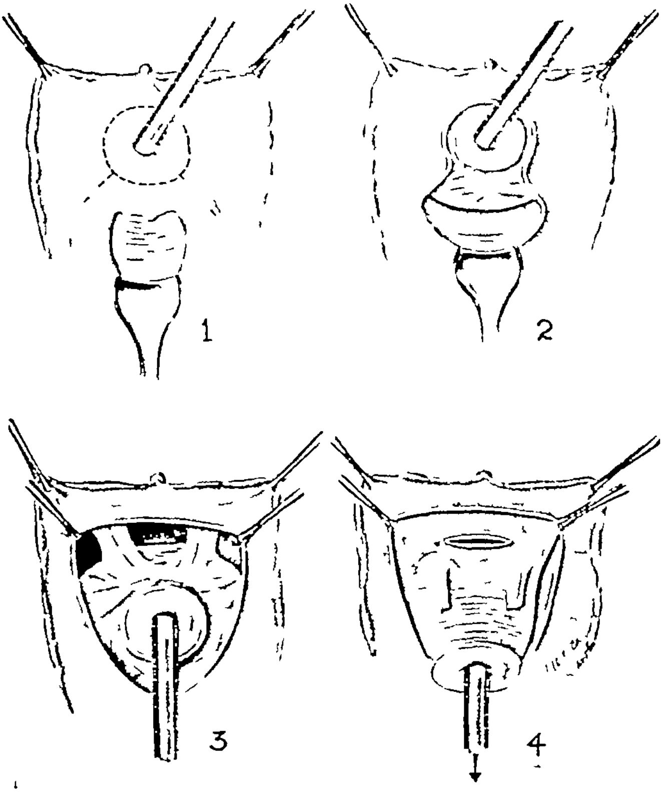

FIG 1 Surgical technique

of total cystourethrectomy with transplantation of the ureters[10] and even radical pelvic exenteration In short, almost all methods and combinations of cancer therapy have been used, and none has been entirely satisfactory Among the few patients who have been cured, the method of treatment has been as varied as it has been in the failures

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[19] Nora, M Epithelioma of the female urethra Total urethrectomy Secondary restoration of the urethra Results nine months after intervention Bull de la Soc Franc d'Urol , pp 147-151, 1929

[20] Roth, A A Carcinoma of the female urethra Ohio State Med J , **51** 872-874, 1955

A question might be raised about the possibility of unrecognized bladder tumors developing in the bladder which has been closed from below Dean[11] emphasises that primary tumors of the urethra are rarely associated with tumors of the bladder In addition, as in the case to be presented, cystoscopy can be performed periodically with relative ease through the cystostomy site

REPORT OF CASE

Mrs L S, age 53, was hospitalized for the care of edema and ulcerations of her lower extremities Thirty-two years previously she had had multiple pelvic operations followed by peritonitis and thrombosis of deep pelvic vessels Since then she had been hospitalized repeatedly for edema of both lower extremities with stasis ulcerations

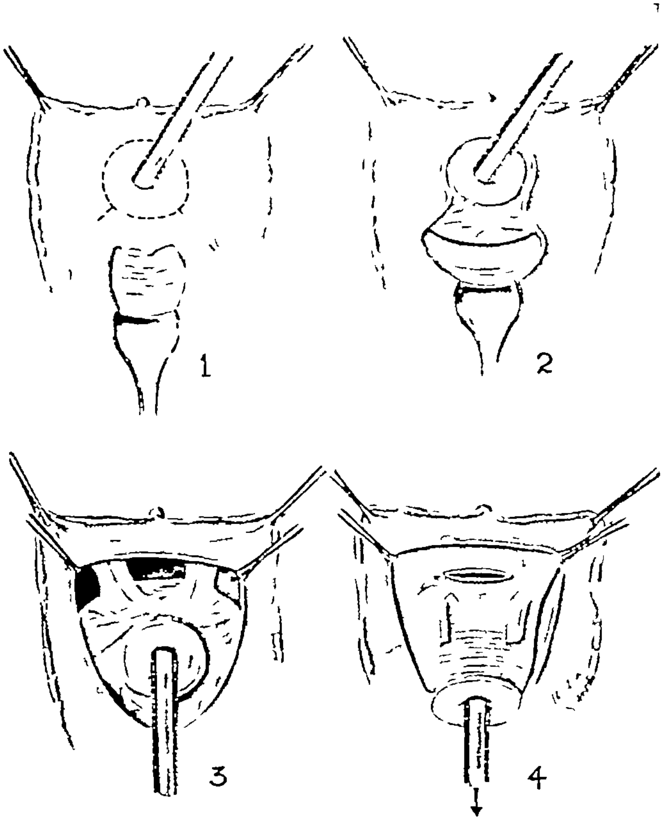

FIG 1 Surgical technique

Her urologic complaints consisted of nocturia 1 to 3 times for many years During the preceding 4 to 6 months she noted marked day frequency with urgency and urgency incontinence She denied any difficulty in voiding but occasionally noted a sense of incomplete empting She complained of no dysuria, gross hematuria or passage of calculi

Physical examination revealed no enlargement or tenderness of either kidney The external urethral meatus was markedly stenosed but otherwise appeared normal Palpation of the inguinal lymphatics was impossible due to massive edema

A catheterized specimen of urine was normal and all laboratory tests including hemogram and blood chemistry studies were within the limits of normal An excretory urogram was grossly normal

At cystoscopy an extremely tight external urethral meatus was noted which required dilatation with sounds before the cystoscope could be passed Unusually heavy bleeding followed the dilatation The bladder interior was normal Upon inspecting the urethra a large, fleshy, tumor mass was seen in the proximal one half of the urethra Vaginal palpation of the urethra over the cystoscope revealed a soft tumor mass approximately 2 cm in diameter with no induration or fixation about it The vaginal mucosa was normal

Several days later, under general anesthesia, the resectoscope was introduced and a nodular mass approximately 1 5 cm in size was again seen on the floor of the proximal urethra The mass extended from the vesical neck out to, but not beyond, the midpoint of the urethra

Because of its position it was felt that the tumor could be resected transurethrally without sacrificing the sphincter As the resection progressed, however, it became apparent that the tumor was considerably larger than expected and probably could not be removed entirely transurethrally The pathologist reported the tissue removed to be an infiltrating squamous cell epithelioma, grade 3

Cystoscopy was repeated approximately one month later, and it was obvious that malignant tissue was still present Again it was noted that the tumor tissue was well removed from the vesical neck Bilateral retrograde pyelograms were normal, and the urethral catheters were left in place while total urethrectomy and permanent cystostomy were being considered

It was decided that due to the marked edema of the inguinal regions a Basset type of inguinal node dissection was contraindicated Irradiation therapy was also contraindicated due to the already extensive impairment of circulation

On April 5, 1956 a total urethrectomy and permanent suprapubic cystostomy were performed in the manner to be described Recovery was completely uneventful Three months postoperatively and again 6 months after surgery cystoscopy was performed readily through the suprapubic fistula and revealed the bladder to be normal except for bullous edema due to the indwelling catheter Vaginal examination and palpation revealed no evidence of induration or tumor

OPERATIVE TECHNIQUE

Indwelling ureteral catheters were in place as guides to identify the intramural portion of each ureter A Foley catheter was inserted for traction The

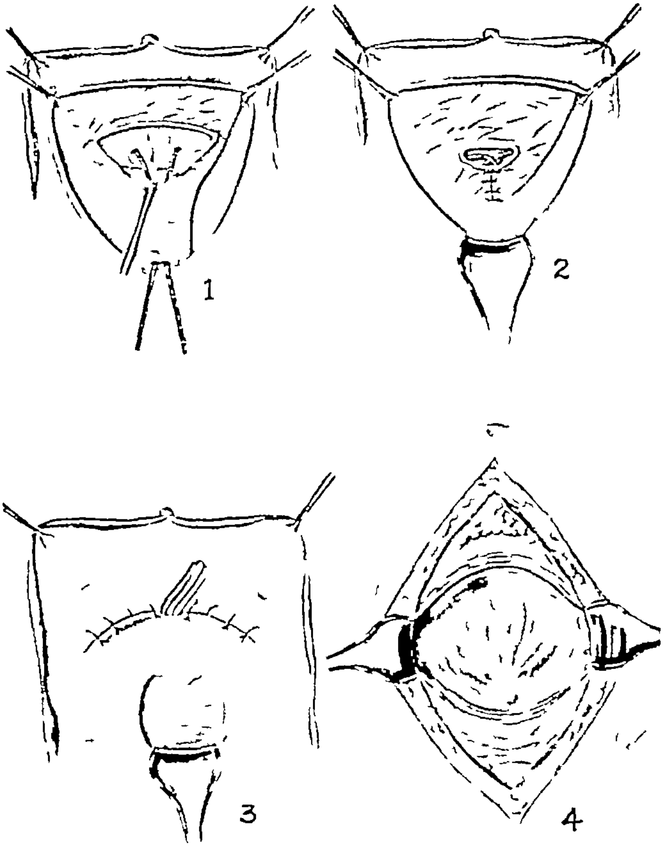

FIG 2 Surgical technique

labia were separated and a circular incision was made about the meatus through the vestibular mucosa The incision was extended laterally and posteriorly on each side (fig 1, *1*)

A cleavage plane was established without difficulty between the anterior vaginal wall and the posterior periurethral tissues (fig 1, *2*), and by blunt dissection the entire posterior and lateral aspects of the urethra were freed easily up to and above the vesical neck

Then, by exerting traction upon the Foley catheter downward and posteriorly (fig 1, *3*), the partially mobilized urethra could be brought forward sufficiently to visualize the pubourethral ligaments These ligaments are quite interesting and in fact have been overlooked entirely in most anatomy texts as well as the standard urology text books Krantz[21] describes them well and refers to them as the "puboprostatic ligaments of the female," emphasizing again the homologous nature of the female urethra and the prostatic urethra in the male

[21] Krantz, K E in Ullery, J C Stress Incontinence in the Female New York Grune and Stratton, 1953, 39 pp

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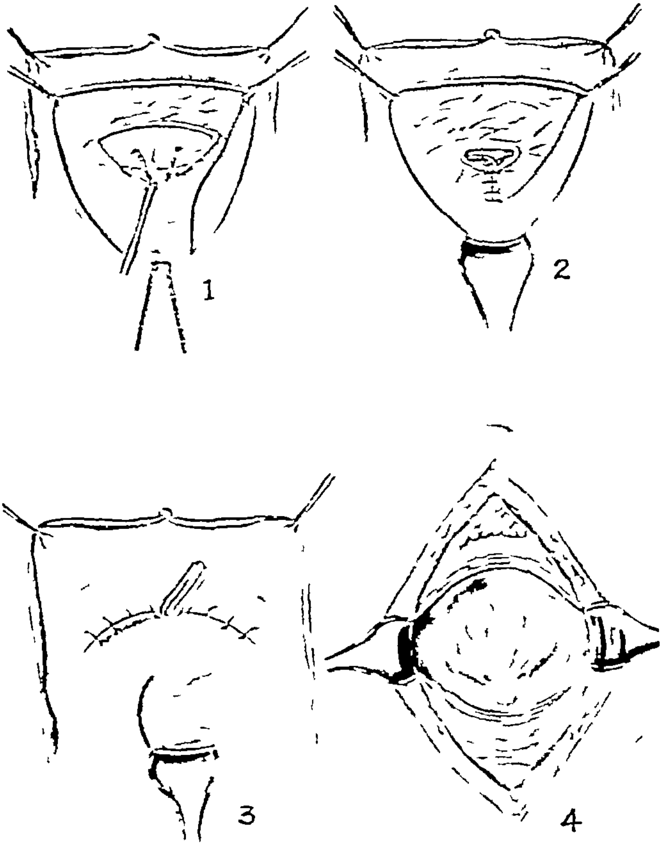

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[a] Krantz, K E in Ullery J C Stress Incontinence in the Female New York Grune and Stratton, 1953 39 pp

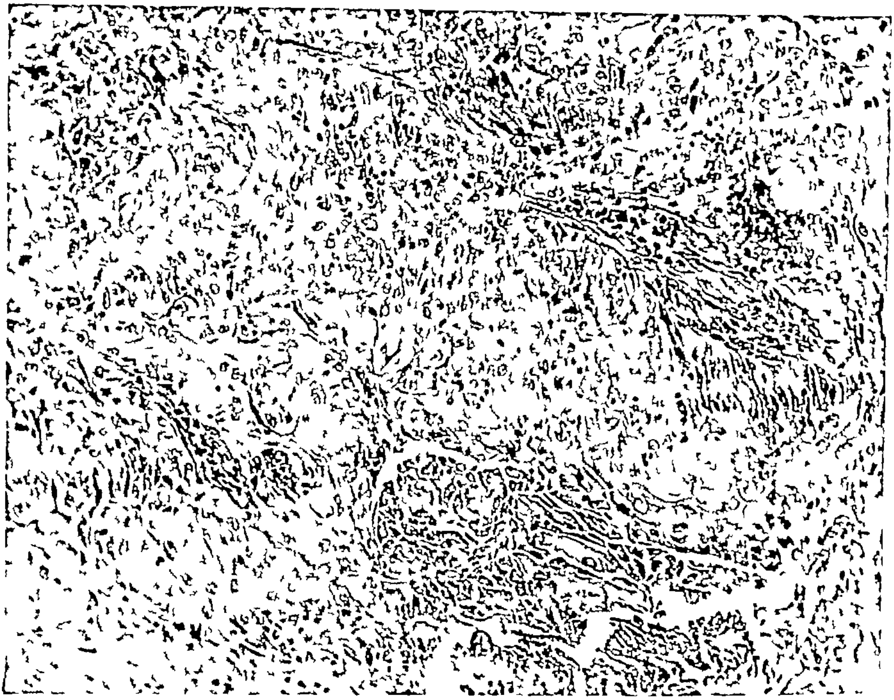

FIG 3 Grade 3 infiltrating squamous cell epithelioma of female urethra

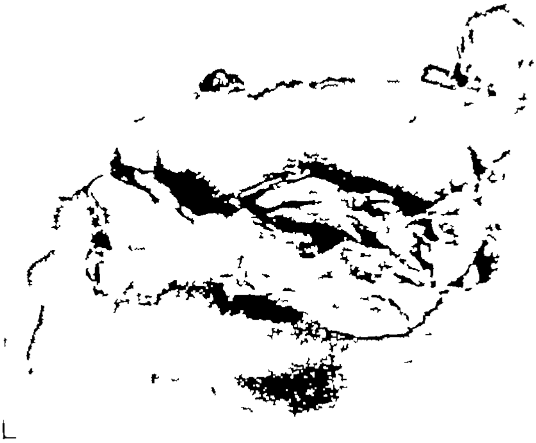

FIG 4 Gross specimen Female urethra opened longitudinally

Severing these ligaments (fig 1, *4*) permitted the entire urethra and lower portion of the bladder to be brought into clear view easily A stab wound was made anteriorly in the bladder wall above the vesical neck and under direct vision extended laterally around the base of the bladder above the vesical neck (fig 2, *1*) The Foley catheter was removed and the ureteral catheters permitted accurate dissection between the vesical neck and the ureteral orifices The bladder base was circumscribed completely and the urethra and vesical neck removed

The ends of the ureteral catheters were coiled in the bladder leaving the catheters in the ureters as extra protection against catching the ureters in a suture while the base of the bladder was sewn up tightly (fig 2 2) The vestibular mucosa was then closed leaving a small drain to the suture line in the bladder (fig 2 3)

The patient s position was then changed and a permanent cystostomy performed With the bladder opened from above the ureteral catheters were removed and the puckered closure of the bladder base could be seen clearly (fig 2 4)

Figure 3 illustrates the grade 3 infiltrating squamous cell epithelioma of the urethra

In figure 4 the entire urethra has been opened longitudinally the external urethral meatus being to the left and the vesical neck to the right Ventrally the rather deep excavation performed transurethrally can be seen The pathologist indicated that there was no malignant tissue within 1 5 cm of the bladder end of the specimen suggesting that the primary growth was removed completely by this procedure

SUMMARY

Carcinoma of the female urethra is not a rare disease and the prognosis is poor Different types and combinations of therapy have been used with generally poor results Total urethrectomy with permanent suprapubic cystostomy is a procedure of merit in selected cases

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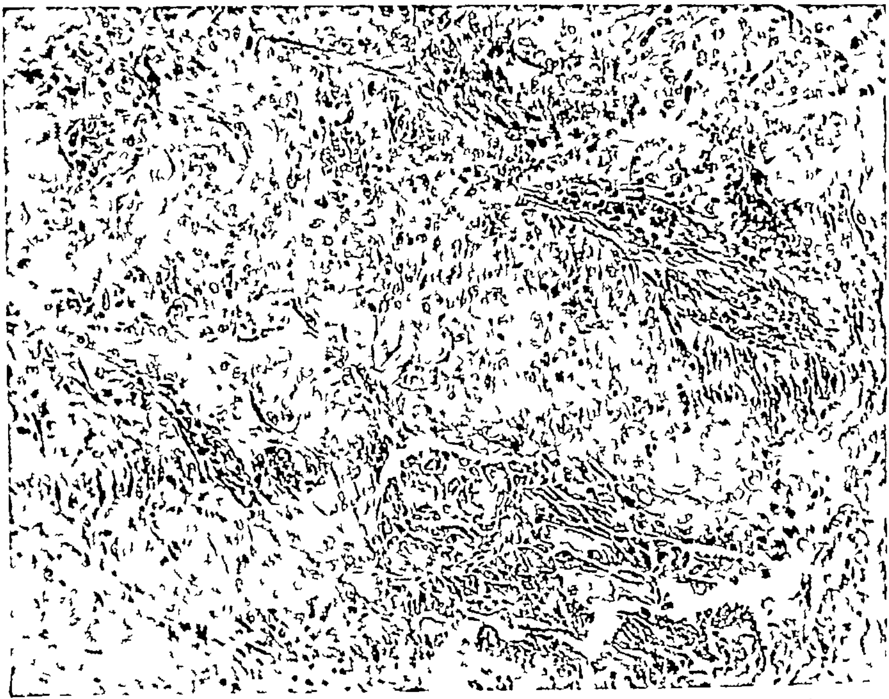

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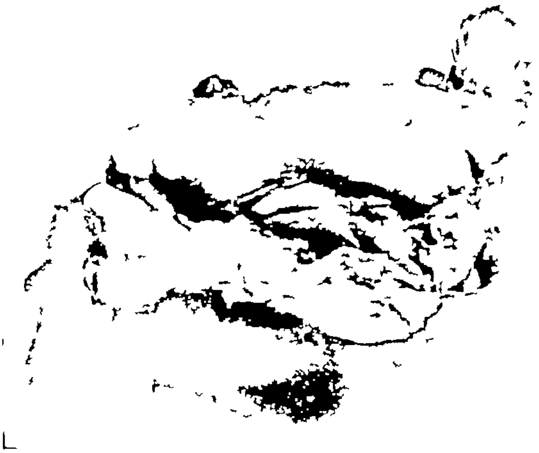

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POLYORCHISM AND CRYPTORCHISM REPORT OF CASE

RICARDO ANGULO AND LUIS CABALLERO
Lima, Peru

The first case of polyorchism was described in 1670 by Blasius who discovered the condition during an autopsy In 1895, Lane presented the first case of polyorchism confirmed histologically

Since then isolated instances have been published in various scientific journals, the latest being that of Saul Kay and F P Coleman who presented the twenty-fifth case in May 1956 In the case here presented the diagnosis was made at operation for right cryptorchism

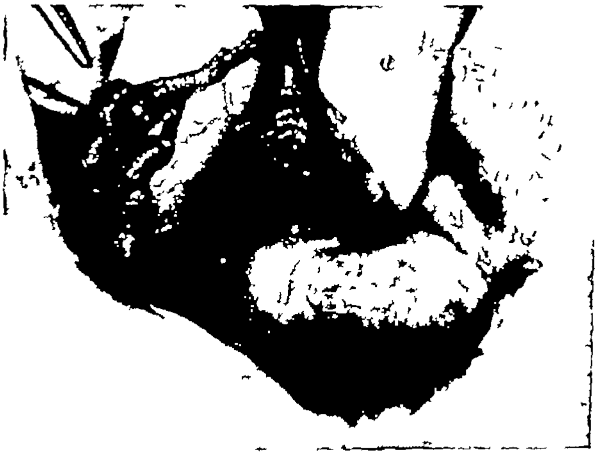

FIG 1

All authors agree that polyorchism occurs most frequently on the left This rare congenital anomaly may be explained embryologically as the persistence of the embryologic nuclei of the primitive gonads which normally degenerate and disappear, being replaced by a nucleus of proliferation at the caudal end of the genital crest of the wolffian body

The interest of our case, which leads us to report it, arises from the concomitance of polyorchism, cryptorchism, varicocele and phimosis and from the fact that we were able to recognize the supernumerary testicle (fig 1) during the operation

CASE REPORT

C M , aged 17, white, was admitted to the Naval Hospital, Lima, Peru March 6, 1956 because of cryptorchism, left varicocele and phimosis

The patient's general appearance was that of a youth of the stated age The significant physical findings were those just mentioned A thick varicocele on the left side and phimosis were present The right testicle appeared to be intra-abdominal since it could not be palpated externally

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On March 8, 1956, under general anesthesia, the varicocele was treated by the method of Branco Ribeyro, and a circumcision was performed A 10 cm incision was made over the right inguinal canal On opening the canal a tubular formation was encountered coresponding to a non-obliterated duct of the tunica vaginalis

Within the duct lay a spermatic cord which formed a large loop and which ended in a conglomerate mass 1 5 cm in length by 1 cm in width It appeared to be an atrophic testicle In freeing the duct of the persistent tunica vaginalis and exerting traction at the level of the neck, a testicle measuring 3 by 2 cm accompanied by its respective spermatic cord and epididymis appeared at the abdominal ring The atrophic testicle was resected and the cord and the sper-

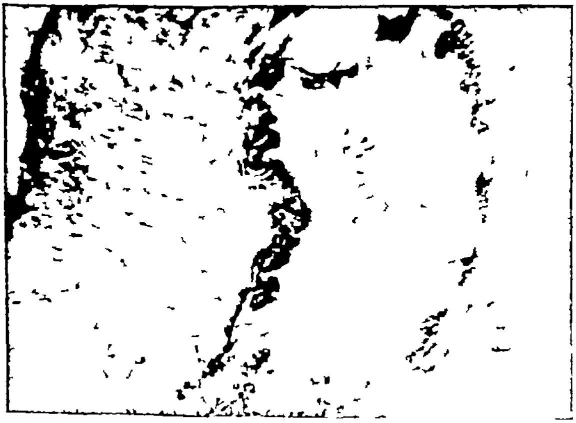

FIG 2

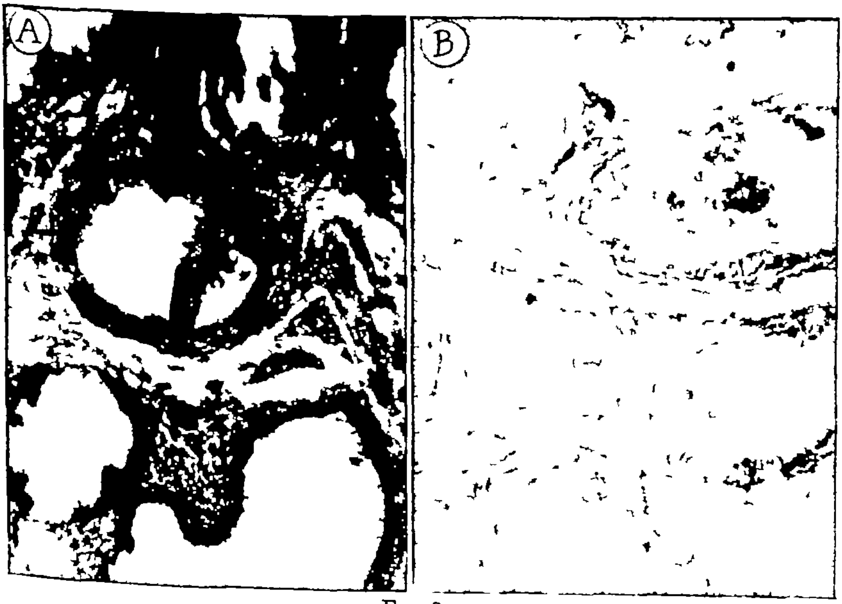

FIG 3

matic plexus were ligated with catgut The peritoneal sac was closed as in herniorrhaphy and the testicle was fixed to the scrotum after the method of Ombrédanne

Pathologist's report The gross specimen consisted of a cylindrical piece of tissue 8 cm in length by 4 mm in diameter Two cubic centimeters of one end were serpiginous, the other end terminated in a superficially granular oval mass 2 by 0 5 cm

The first two portions had a firm consistency, the third was soft

Transverse sections through the first and second portions showed that they were formed by the spermatic cord, whereas the third portion exhibited a finely granular, yellowish-white surface striated in several parts by fibrous tracts

Microscopic anatomy Serial sections were made at 1 cm intervals In the sections from the first portion of the specimen a duct was seen lined by simple cylindrical epithelium with a submucosa consisting of elastic fibers surrounded by a well defined muscular layer, which in turn is covered by serosa The characteristics identified it as a vas deferens (fig 2)

In the sections from the second portion a cavity was seen lined by a double layer of ciliated epithelial cells among which were transitional cells Circular muscle fibers lay outside the epithelium which was in turn covered by serosa The specimen was thus identified as an epididymal duct (fig 3, *A*)

The sections from the third portion exhibited ducts lined with Sertoli cells There was no evidence of spermatogenesis (fig 3, *B*)

Diagnosis *Atrophic testicle and germinal aplasia of epididymis with vas deferens*

Jiron Arica 882, Lima, Peru

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THE RESULTS OF 1,694 CONSECUTIVE SIMPLE PERINEAL PROSTATECTOMIES

RODERICK D. TURNER AND ELMER BELT

From the Elmer Belt Urologic Group and the Department of Surgery, Division of Urology, University of California Medical Center, Los Angeles, Calif.

This study outlines an analysis of the surgical data of 1,694 consecutive patients. The preoperative, postoperative, surgical, pathological, and complication records were transferred to International Business Machine punch cards. The statistics were accurately computed by sorters, tabulators and "101 machines."

Each of the 1,694 consecutive patients underwent a simple perineal prostatectomy between December 31, 1930 and December 31, 1955. While 1,613 had a pathological microscopic diagnosis of benign prostatic hyperplasia, 81 were found to have malignancy of the prostate gland upon microscopic examination of the tissue. Forty-five of these 1,694 patients were admitted to the hospital with a preoperative diagnosis of suspected adenocarcinoma of the prostate. Simple perineal prostatectomy was done in most of these patients with carcinoma if the capsule was found to be adherent or if the rapid frozen section biopsy was negative. Some proved positive for adenocarcinoma on later paraffin sections. In some patients having carcinoma of the prostate, and when tumor was obviously beyond the limits of total perineal removal, a simple enucleation was done to relieve obstruction.

Thirty-six of the 81 patients with a diagnosis of carcinoma had a microscopic report revealing a localized neoplasm within benign prostatic hyperplasia. All of these 81 cases were excluded from this study, due to the presence of malignancy, but their survival rate is described by Belt[1] in malignancy of the prostate gland.

CHOICE OF SURGICAL APPROACH AND TECHNIQUE

The choice of surgical approach has been discussed clearly by Davis and Lee.[2] We agree with the rationale in their selection of this type of surgery. If left to the authors' preference, the perineal route is felt to afford less surgical and postoperative shock, thus permitting the surgeon the freedom to elect total removal if indicated by exploration or biopsy.

We differ with Davis and Lee[2] as to the actual surgical technique used in the in the operation, feeling that the approach between the anal sphincter and the rectum affords a definite anatomical and bloodless approach to the prostate, with less chance of injury to the rectum because with this approach the rectum is under direct observation throughout the entire procedure.

Blood loss during and after surgery is much more readily controlled using the

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Read before Section on Urology at annual meeting of American Medical Association, Chicago, June 13, 1956.

[1] Turner, R. D. and Belt, E.: Study of 229 consecutive cases of total perineal prostatectomy for cancer of prostate. J. Urol., 77: 62, 1957.

[2] Davis, E. and Lee, L. W.: Progress in perineal prostatectomy. Results in 2050 consecutive patients. J. Urol., 73: 142, 1955.

modified Belt[3] approach Hence by this method perineal hematomas are seldom seen The specific indications for perineal surgery are listed below

INDICATIONS FOR SIMPLE PERINEAL PROSTATECTOMY

1 Medium size to large adenomas
2 Very obese patients
3 Patients of poor risk or elderly
4 When a nodule suspected of being malignant is present, biopsy with rapid frozen section can be done, and choice of simple or total approach may follow
5 Patients presenting hematological problems are selected for perineal operation because with this approach freedom from hemorrhage is more certainly attained

ANESTHESIA AND POSITION OF THE PATIENT

A hypobaric spinal anesthetic is the most satisfactory anesthetic because the patient is placed in the accentuated lithotomy position and the anesthesia produced does not interfere with respiration If it is necessary because of advanced arthritis or neurological disorders to use general anesthesia, endotracheal intubation is advised because of the Trendelenburg position of the patient which may embarrass respiration

When the anesthetic level has become fixed, care is taken to cushion the supported legs to avoid nerve trauma The surface of the perineum should be parallel to the floor

CONVALESCENCE

The Penrose drain is removed within 24 hours and the patient permitted to be ambulatory All dressings are removed Dry heat is applied to the perineum twice daily beginning on the second postoperative day The catheter is removed within eight days, if the bowels have moved If, when the catheter is removed, there is perineal drainage which does not show signs of lessening, the catheter may be reinserted for several days Hot, moist dressings are applied three times daily to the perineum if the wound edges show evidence of inflammation The preoperative and postoperative orders are described in the total perineal prostatectomy by Belt [1] The patient is usually discharged on an average of the ninth day Weekly office visits are encouraged during the first six postoperative weeks The condition of the perineum, stream, control, convalescence, and general health are followed carefully It has been found that it is easier to obtain co-operation from those patients who have had prostatic malignancy and were advised of this fact than from those who had a benign process

PREVIOUS PROSTATIC SURGERY

One hundred and nineteen patients (7 4 per cent) underwent transurethral resection of the prostate gland prior to simple perineal prostatectomy (table 1) Three patients had submitted to previous perineal prostatectomy with regeneration of prostatic adenoma, and seven (0 4 per cent) patients underwent a suprapubic prostatectomy before requiring the final simple perineal prostatectomy This is a total of 129 (8 0 per cent) patients who had had previous prostatic

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[3] Belt, E , Ebert, C E and Surber, A C A new anatomic approach in perineal prostatectomy J Urol , 41 482, 1939

TABLE 1 *Weight of tissue enucleated in patients who had undergone previous prostatic surgery*

No of Patients	Grade I 10-25 gm	Grade II 26-50 gm	Grade III 51-100 gm	Grade IV > 100 gm	Total
TUR	35	38	36	10	119
Suprapubic	5		2		7
Perineal	2		1		3
					129

surgery The technical procedure at surgery presented no special difficulty in any individual of this group of patients[4]

URETHRAL STRICTURE AND CONTRACTURE OF BLADDER NECK

A Preoperative One hundred and thirty-one patients (8 1 per cent) had a preoperative diagnosis of urethral stricture Eighteen of these (1 4 per cent) had had previous prostatic surgery seventeen had had preoperative transurethral resection, and one had had a previous simple perineal prostatectomy

Sixty-seven patients (4 2 per cent) had a diagnosis of contracture of the bladder neck prior to simple perineal prostatectomy Nine patients (1 3 per cent) had had previous prostatic surgery, seven had had transurethral resection of the prostate, one had had a suprapubic prostatectomy, and one had had a perineal prostatectomy

B Postoperative In sixty-four (3 9 per cent) additional patients urethral stricture or contracture of the bladder neck followed simple perineal prostatectomy Five patients (0 3 per cent) required an additional transurethral resection of the bladder neck remotely subsequent to perineal surgery In checking the aforementioned patients carefully, no correlation was found between the size of adenoma or the age of the patient in relation to the degree of postoperative urethral stricture, or contracture of the bladder neck

INCIDENCE OF OTHER GENITOURINARY TRACT DISEASE IN 1,613 PATIENTS UNDERGOING SIMPLE PERINEAL PROSTATECTOMY

A diagnosis of unassociated cancer in some other location in the genitourinary system was made in 48 patients (3 0 per cent) of the 1,613 with benign prostatic hyperplasia (table 2) The types of tumor included hypernephroma, bladder tumors, and many others

One hundred and twenty-three patients (7 6 per cent) had a history of urinary tract calculi (table 2) Extraction of vesical calculi at the time of perineal prostatectomy was accomplished in many cases without difficulty, but marked pyelonephritis accompanied a few of these additional procedures

Only one patient in the entire group had active tuberculosis in the genitourinary tract (table 2)

One hundred and eight patients (6 8 per cent) had diseases of the testes or

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[4] Goodwin W E Radical prostatectomy after previous prostatic surgery J A M A, 148 799 1952

TABLE 2 *Other urological disease in 1,613 patients having perineal prostatectomy*

	No of Patients	Per Cent
Urinary calculi	123	7 6
Scrotal diseases—tumor, varicocele, hydrocele, epididymitis, etc	108	6 8
Unassociated genito urinary cancer	48	3 0
Tuberculosis (active)	1	

epididymides, such as hydrocele, varicocele, spermatocele, epididymitis, epididymo-orchitis, gumma of the testicle, inactive tuberculosis, and others

GENITOURINARY (EXTRAPROSTATIC) SURGERY PERFORMED BEFORE OR AFTER SIMPLE PERINEAL PROSTATECTOMY IN 1,613 PATIENTS

Seventy-nine patients (4 9 per cent) subsequently underwent scrotal surgery * Seventy-seven (4 8 per cent) underwent bladder surgery (suprapubic, transurethral, etc , not including cystotomy) Thirty (1 9 per cent) submitted to renal surgery (nephrectomy, pyelolithotomy, etc) Ureteral surgery (plastic, ureterolithotomy, etc) was performed in 18 patients (1 1 per cent)

DIVISION INTO FOUR GROUPS BY WEIGHT OF TISSUE (ADENOMA) ENUCLEATED AT SURGERY

The rectal estimate of size is not used for comparative analysis in this study The recorded weight of the surgical specimen is the figure used Group 1 represents adenomas ranging up to 25 gm in weight Group 2 includes enucleated tissue weighing between 26 and 50 gm In group 3 patients, the weight falls between 51 and 100 gm , and group 4 includes patients from whom 100 gm or more of adenoma were removed at surgery

It is of interest to observe that a higher degree of accuracy was attained in the group 2 and group 3 sizes, on comparing the preoperative rectal examination estimate, with the weight of the enucleated tissue (figs 1 and 2) As the patients grew older the weight of prostatic tissue enucleated rose proportionately (table 3) Older age groups have no added morbidity so that now most of the patients operated on are over 60 years of age (fig 3)

COMPARISON OF THE FOUR SIZES BY WEIGHT OF TISSUE ENUCLEATED

A Previous prostatic surgery Patients who had previously undergone transurethral prostatic resection presented themselves with adenomas of all sizes as the following grouping shows Thirty-five patients (7 2 per cent) out of 492 in group 1 having had a previous transurethral prostatic resection were found to have between 10 and 25 gm enucleated at perineal prostatectomy Thirty-eight patients (7 0 per cent) out of 544 of those in group 2 who had undergone a previous transurethral resection had 26-50 gm removed by the perineal route In 36 patients (8 4 per cent) out of 429 who had had a previous transurethral prostatic

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* Fifty two patients (3 2 per cent) had additional scrotal surgery at the same time as the simple perineal prostatectomy Incision and ligation of the vas deferens which are not included in this group are routinely done at the time of prostatectomy

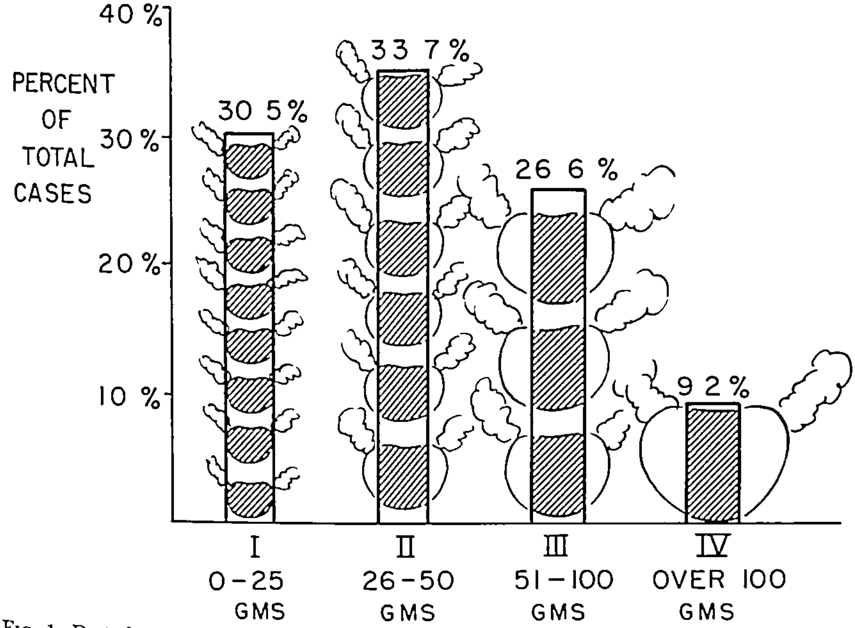

Fig 1 Distribution of weight of surgical specimens in 1 613 cases of simple perineal prostatectomy

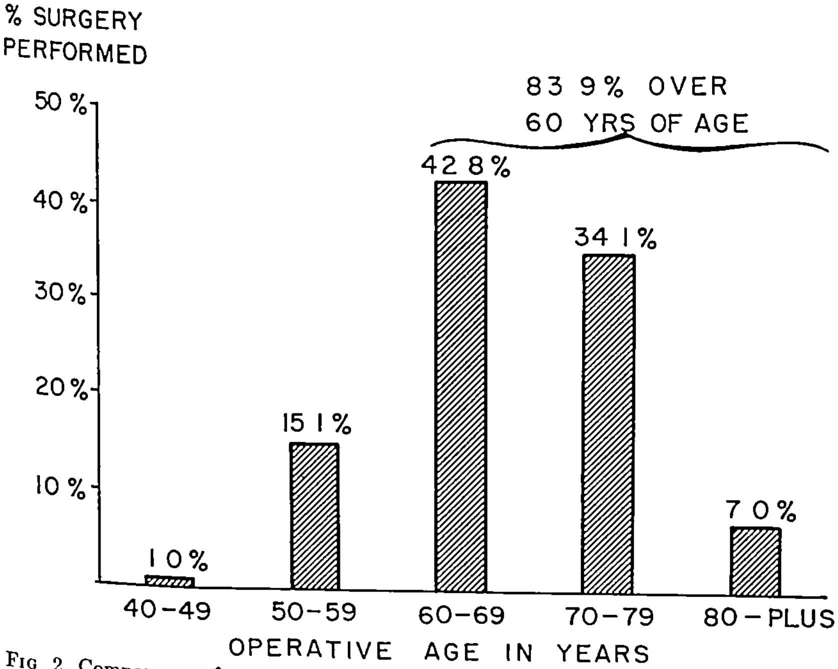

Fig 2 Comparison of preoperative estimated size with weight of surgical specimen in 1 613 cases

TABLE 3 *Relationship of age at operation to weight of adenoma removed*

Weight of Adenoma	Operative Age in Years				
	40–49	50–59	60–69	70–79	80 plus
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
I, 0–25 gm	2 5	23 9	47 1	22 7	3 8
II, 26–50 gm	0 5	16 3	46 2	32 0	5 0
III, 51–100 gm	0	8 0	37 9	44 7	9 4
IV, over 100 gm	0	2 0	30 0	49 5	18 5

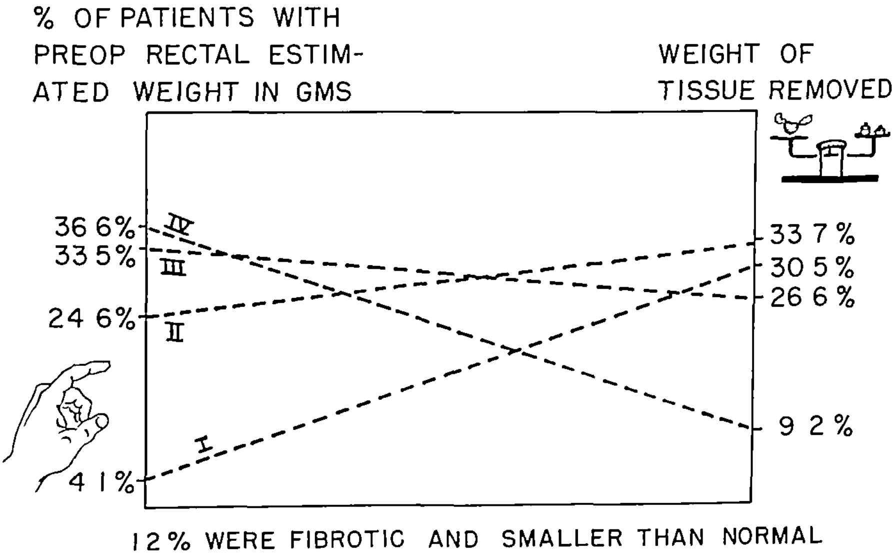

FIG 3 Age incidence in 1,613 cases of simple perineal prostatectomy

resection, between 50 and 100 gm adenoma were enucleated at perineal prostatectomy Ten patients (5 8 per cent) out of 148 in group 4 had more than 100 gm enucleated at perineal prostatectomy after previous transurethral resections Of the 3 patients who had simple perineal prostatectomies performed prior to final perineal surgery, two had between 10 and 25 gm enucleated while one had 51 gm removed Five patients, who had had a previous suprapubic prostatectomy, had between 10 and 25 gm removed perineally Two patients, who had previous suprapubic enucleation, were found to have 87 gm and 62 gm , respectively, when this tissue was finally removed by perineal prostatectomy

POSTOPERATIVE INCONTINENCE IN 1,613 PATIENTS

Ninety-five patients (5 9 per cent) had temporary incontinence for less than one year Thirty patients (1 9 per cent) had persistent incontinence There was no variation in the incidence of incontinence in respect to the size of the adenomas enucleated One patient in whom incontinence followed a previous suprapubic prostatectomy regained complete urinary control after submitting to simple perineal prostatectomy

POSTOPERATIVE BIOPSY IN 1,613 PATIENTS

A biopsy by means of transurethral resection was obtained in 2 cases after perineal prostatectomy because nodules at the bladder neck were suspected of being malignant. These nodules appeared 8 and 10 years later respectively. Two patients in whom nodules developed at the bladder neck postoperatively were subjected to open perineal biopsy each 6 years later. All four biopsies were reported benign.

IMPOTENCE

Sexual impotency as a possible postoperative sequel after open perineal removal of the prostate is freely discussed with this group of elderly patients preoperatively. An understanding of the possible eventuality of sexual impotence is reached before operation. This understanding results in greater contentment should this complication arise. A statistical evaluation of sexual impotence following surgical removal of the prostate is difficult to set forth because of the difficulty in collecting realistic data. In general we have noted that in our retropubic prostatectomy series this function remains active during the early postoperative months but fades away rapidly as the venous channels reopen and congestion of the penis grows less, usually within six to eight months after operation. The reverse is true in this series of perineal prostatectomies. Early loss of sexual power is often followed by recovery of this function three to six months after operation.

INCIDENCE OF EPIDIDYMITIS IN 1,613 PATIENTS

Eighty-six (5.3 per cent) out of 1,613 patients who underwent simple perineal prostatectomies and bilateral ligation of the vas deferens acquired epididymitis (table 4). All but five of these operations were performed before the advent of antibiotics and sulfonamides. There was a higher incidence of epididymitis in the younger age group at the time of surgery.

Nine per cent of the patients between 50 and 59 years of age acquired postoperative epididymitis. Only 1.8 per cent of patients over 80 years of age had this complication. Our figures parallel the incidence of epididymitis in other forms of prostatic surgery.

TABLE 4.—*Incidence of epididymitis in 1,613 cases of simple perineal prostatectomy*
Overall incidence of epididymitis = 5.3% (86 cases)

Distribution of All Cases of Epididymitis	Years				
	[illegible]	50–59	60–69	70–79	80 plus
		per cent	per cent	per cent	per cent
By operative age	0	9.1	5.2	4.7	1.8
	Grade				
	I <25 gm.	II 25–50 gm.	III 51–100 gm.	IV >100 gm.	
	per cent	per cent	per cent	per cent	
By weight	3.2	5.8	6.0	3.0	

TABLE 5 *Complications at surgery, 1,613 patients*

Complication	No of Cases	Per Cent
Excessive hemorrhage	41	2 54
Perforation of rectum	5	0 31
Cardiac—anesthetic difficulty	1	0 06

TABLE 6 *Postoperative complications in 1,613 cases of simple perineal prostatectomy*

Complication	No of Patients	Per Cent
Epididymitis	86	5 33
Hemorrhage	48	2 98
Perineal fistulas	9	0 56
Breakdown of incision, suture	8	0 50
Breakdown of incision, infection	7	0 43
Perineal abscess	8	0 50
Acute retention	6	0 37
Contracture of bladder neck	5	0 31
Pyelonephritis	5	0 31
Postoperative residual >60 cc	4	0 25
Operative shock	3	0 19
Ureteral obstruction (ligation)	1	0 06
Perineal hematoma	1	0 06

DISTRIBUTION OF EPIDIDYMITIS BY SIZE OF ADENOMA

There was a higher degree of epididymitis among patients with middle-sized enucleated adenomas than among those with very small or very large glands (table 5) Approximately 3 0 per cent of all patients with enucleated adenomas weighing between 10 and 25 gm acquired epididymitis, while 3 9 per cent of those with enucleated adenomas weighing over 100 gm also had epididymitis The two middle weight groups definitely had a higher morbidity due to the occurrence of epididymitis

COMPLICATIONS AT SURGERY IN 1,613 PATIENTS

Forty-one patients (2 5 per cent) in the overall series of 1,613 simple perineal prostatectomies had troublesome bleeding during the surgery recorded in the operative dictation (table 5) Five patients (0 3 per cent) had perforation of the rectum recognized at the time of the surgery Ninety per cent of these operative problems occurred in the earlier cases in the years between 1930 and 1945 If laceration of the rectum is recognized on entry to the prostate gland before the biopsy or capsule is incised, the procedure of prostatectomy is discontinued The rectal laceration is closed in two layers with 00 G-I atramatic interrupted sutures The prostatectomy is done one to two weeks later transurethrally This allows ample time for the rectal laceration to heal During this healing period the patient is placed on oral neomycin ½ gm , b i d for 10 days and sulphasuccidine or sulfaguanidine, gm 1, q i d for 4 weeks Two tablespoons of mineral oil and cathartics of choice are given at bed time Constipation is thus averted

If laceration of the rectum, which is a rare occurrence, is recognized only after the prostatectomy has been completed the program just described is followed with the exception that the indwelling Foley catheter is now left in place for 8 days to prevent urine seeping into the perineum before the rectal laceration has healed The Penrose drain is also left in place for one week, or longer if drainage continues The manner in which wound healing proceeds determines the action in regard to the length of time the catheter is to be left in place or the Penrose drain is to be left in the wound If drainage seems to be adequate and no pocketing is noted, it is well to remove all drains from the wound early Should a fistula form and persist between the prostatic urethra and the rectum associated with perineal drainage through the wound the resulting sinuses may be expected ultimately to heal spontaneously Final closure may take several weeks Because the rectal sphincter has been elevated and the fistula does not ride over the sphincter but runs along below it, spontaneous healing is invariable for healing is assisted rather than delayed by the occlusive pull of the sphincter

POSTOPERATIVE COMPLICATIONS IN 1 613 PATIENTS

These have been itemized in table 6

Over three-quarters of the patients with bleeding were in the early group of cases operated on between 1930 and 1945 Bleeding is not a problem at the present since it has occurred only once in the past 200 operations

TABLE 7 *Average days of hospitalization*

Age in Years	Grade (Weight)				Ave No of Days by Age
	I. 0-25 gm.	II. 26-50 gm	III 51-100 gm.	IV > 100 gm	
40-49	11 0	9 5			10 2
50-59	11 3	9 6	10 6	11 2	10 7
60-69	11 4	11 4	11 0	11 5	11 3
70-79	11 5	12 1	11 9	11 6	11 7
80 plus	11 3	11 1	12 3	12 4	11 8
Ave no of days by grade	11 3	10 7	11 4	11 7	11 2

No selection—all 1,613 cases included

TABLE 8 *Transurethral prostatic surgery following 1 613 simple perineal prostatectomies*

No of Patients	Weight of Tissue Removed at Simple Perineal Prostatectomy	Reason for Repeat Prostatic Surgery	No of Yrs after Simple Perineal
	gm		
3	10-25	Contracture of bladder neck	2 mos 1 yr 3 yrs
1	26-50	Contracture of bladder neck	1
1	51-100	Contracture of bladder neck	2
1	10-25	Recurrent adenoma	12
2	26-50	Recurrent adenoma	8 5

HOSPITALIZATION

The average number of hospital days has diminished from an average of 13 during the period 1930–1940 to an average of 9 days during the period 1950–1955 (table 7) Increasing familiarity with surgical techniques, antibiotics, and improved post-surgical management all assist in the early discharge of patients with their catheters removed and their perineums dry with good control The average stay in hospital was not affected by the size of the adenoma enucleated The patients whose ages were between 40 and 50 years and who had between 26 and 50 gm of prostatic adenoma enucleated were hospitalized the least number of days

TABLE 9 *Transurethral resection required after simple perineal prostatectomy for benign hypertrophy in subsequently obstructing adenocarcinoma*

Number of Patients	Weight of Tissue Enucleated at Simple Perineal Prostatectomy	T U R P Microscopic Report	Number of Years Later
	gm		
2	10–25	Adenocarcinoma (benign at simple perineal)	2 7
3	26–50	Adenocarcinoma	3 8 11
1	51–100	Adenocarcinoma	13
1	Over 100	Adenocarcinoma	11

TABLE 10 *Distribution of pathological process reported microscopically in 1,613 patients*

	No of Cases	Per Cent
Benign prostatic hyperplasia	909	53 3
Benign prostatic hypertrophy with prostatitis	586	36 3
Benign prostatic hypertrophy with calculi	56	3 5
Suppurative prostatitis	46	2 8
Fibroma	11	0 7
Prostatic abscess	4	0 3
Tuberculosis	1	0 1
Total	1,613	100 0

TABLE 11 *Hospital mortality rate*

Death Certificate Cause	No of Patients
Cardiac	14
Pulmonary embolus	11
Cerebral thrombosis	7
Pneumonia	5
Gastrointestinal	5
Shock	4
Septicemia	1
Carcinoma, bladder ruptured	1
Total	48 = 2 9%

TRANSURETHRAL RESECTION FOLLOWING SIMPLE PERINEAL PROSTATECTOMY

A higher incidence of contracture of the bladder neck occurred in the small glands (table 8) Three patients who had recurrent adenomas following simple perineal prostatectomy underwent transurethral resection an average of more than 8 years later In 7 patients adenocarcinoma developed after simple perineal prostatectomy an average of almost eight years later, which was sufficiently obstructive to necessitate transurethral resection (table 9) In this series postoperative study of the tissue disclosed suppurative prostatitis bordering on abscess formation in 46 patients (2 8 per cent) Fifty-six patients (3.5 per cent) had prostatic calculi removed at the time of surgery It surprised us to find only one case of active tuberculous prostatitis in this entire series However, there were many seemingly healed tuberculous lesions among the prostatic specimens but tubercle bacilli could only be obtained in one patient by acid fast stain, culture, and guinea pig inoculation (table 10)

HOSPITAL MORTALITY RATE IN 1,613 PATIENTS

A hospital mortality rate of 2 9 per cent (48 patients) was found (table 10) Postoperative shock and septicemia occurred in 5 patients and was believed to be directly attributable to the perineal surgery Forty-one (85 per cent) of the 48 hospital deaths occurred prior to 1945 See table 11

DISCUSSION AND SUMMARY

Simple perineal prostatectomy allows the surgeon an anatomically precise surgical approach It is accompanied by very little morbidity and mortality It still affords the older age group and cardiac cripples a minimally shocking procedure This operation, which lasts on an average of forty-five minutes, permits minimal shock It is virtually free of operative and postoperative hemorrhage, a complication which adds to the morbidity in other forms of prostatic surgery As with all types of surgery, the complications become less with time and experience Therefore, simple perineal prostatectomy has a definite place in removing adenomas of all sizes and all pathological conditions An advantage is that it allows the operator the opportunity to procure material for a rapid frozen section from capsular nodules suspected of being malignant If prostatic cancer is found, the stage is set for total removal

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PROSTATIC ADENOCARCINOMA (MEDULLARY TYPE)

CHARLES G WELLER

Soft types of carcinoma of the prostate gland are uncommon They are of importance chiefly because of the diagnostic difficulties which they present

Dr Hugh Young described five such tumors encountered over a period of ten years (1912 to 1921, inclusive) at the Brady Urological Institute, none of which were correctly diagnosed preoperatively He felt that "in the prostate it is not possible to distinguish different kinds of carcinoma It will be found that there are several different types of growth which cannot represent different tumors since various combinations of them may be found in an individual case All prostatic cancers are adenocarcinomatous in nature " Young divides the soft carcinomas into three types (1) an infiltrating growth in which the cells, apparently growing faster than usual, collect in masses or separate the connective tissue and muscle fibers so much that no firm stroma is present (a picture which may be called medullary carcinoma), (2) glandular or tubular carcinoma in which the elements are close together, separated only by minimal amount of stroma, (3) large areas of intra-acinous proliferation where no stroma is present

Since Dr Young's publication in 1926, there have been only sporadic reports until the paper read before this Section by Dr G J Thompson in 1951, in which he reported fifteen cases of well authenticated squamous cell carcinoma of the prostate, six cases of extension of rectal adenocarcinoma, one mucoid adenocarcinoma and one adenocarcinoma metastatic from the stomach All of these were soft types of neoplasm He stated, "In the majority of cases, the smooth, soft consistency of the prostate gland led the examiner to believe that a malignant lesion was not present " He also observed that in these cases hormonal therapy was ineffective, serum acid phosphatase was not elevated, and that the survival period was comparatively short

We wish to record three cases of the medullary type of adenocarcinoma of the prostate, the first of which was seen shortly before the advent of hormonal therapy, and was misdiagnosed preoperatively as benign prostatic hyperplasia Suprapubic enucleation was attempted, but the tissue was so soft that it was removed with a gallbladder spoon in slightly yellow-white, waxy lobules of low vascularity resembling in consistency fresh pancreatic tissue The second and third were approached transurethrally and cut like soft cheese with little bleeding

These tumors had in common certain unique characteristics On rectal palpation, the tumor was smooth and soft, giving the impression of tense fluctuation The borders were clearly demarcated Induration was not noted in the region of the seminal vesicles Cystoscopically, the mucosa was smooth, or yellow-white, edematous, rounded tumor masses were seen, especially in the bladder floor In cases 2 and 3 the serum acid phosphatase was not elevated nor was growth inhibited by hormonal therapy All recurred with extreme rapidity and the patients died within a few months

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Read at the annual meeting of the North Central Section of the American Urological Association, Cleveland, Ohio, October 3-5, 1956

Case 1 A man in his late 60's was considered preoperatively to be suffering from benign prostatic hyperplasia and suprapubic prostatectomy was attempted The original record has been misplaced, but I recall the following Digital removal of the neoplasm was not possible because of its soft consistency necessitating the use of a gallbladder spoon to complete the procedure Bleeding was minimal The resident, in attempting to elevate the prostate per rectum broke through the wall into the prostatic cavity because of the friability of the tissues This did not pose much of a problem as the rapid growth of the tumor closed the fistula in less than a week One month postoperatively at the time of the patient's death, recurrent tumor tissue was protruding from the suprapubic fistula Pathological diagnosis by Dr George Rukstinat of Chicago Illinois was medullary carcinoma of the prostate gland

Case 2 G H , age 58 years, consulted us January 20, 1953 He gave a history of transurethral electroresection of a median bar in 1949 which was reported as benign During the preceding three weeks, he complained of an increase of nocturia from none to twice nightly and of diurnal frequency from every four to every one and a half hours He had not experienced chills or fever On examination, the prostate was tense rounded and smooth on the rectal surface and was very sensitive to palpation On February 6 the left lobe had become greatly enlarged smooth and softer than the usual benign hyperplasia Cystoscopically the left lobe displaced the urethra to the right and extended upward into the bladder It was smooth and covered with intact mucosa The right lobe was involved little if at all The acid phosphatase level was normal A soft malignancy was suspected and diethylstilbestrol 1 0 mg t i d was prescribed On February 25 transurethral prostatic resection was performed The tissue cut like soft cheese and with minimal bleeding Thirty-eight grams were removed Pathologic report by Dr P T Dolan of Copley Memorial Hospital Aurora Illinois was "Specimens from the left lobe of the prostate are soft and medullary in consistency and are more deeply charred than those from the right which are firm and pale Microscopically, sections from the right lobe show epithelial but mainly muscular hyperplasia Sections from the left lobe are entirely replaced by tumor and large areas of necrosis Tumor survives mainly about the blood vessels Tumor cells are quite varied in appearance These cells are sometimes large, polygonal with foamy or clear cytoplasm Here the nuclei tend to be large and contain prominent nucleoli In other areas the cytoplasm tends to be solid in appearance and the nuclei smaller, more chromatic and uniform in size This type of cell tends to be fusiform and to resemble somewhat tumor of connective tissue origin This type of tissue is sometimes called carcinosarcoma "

On March 30, the patient experienced urinary retention with intravesical bleeding The prostatic bed was filled with what appeared to be sloughing tissue It extended well up into the bladder This was removed transurethrally and microscopic study showed anaplastic carcinoma with necrosis On April 22, additional large amounts of tumor tissue were removed At autopsy on April 28, 1953 the bladder was almost entirely filled with necrotic tumor tissue reaching 10 0 cm above the symphysis pubis Pathologic diagnosis was "Medullary carcinoma of largely necrotic However, the nuclei are generally well preserved and these are highly anaplastic Many bizarre forms are seen as well as numerous mitotic figures In general, the tumor appears much more anaplastic than reported in previous biopsies It occurs in large sheets of cells almost to the exclusion of other types of tissues" (figs 1 and 2)

Case 3 A L, a 64-year-old white man, had been under treatment with diethylstilbestrol, 1 0 mg t i d, since August 1949, because of prostatic adeno-

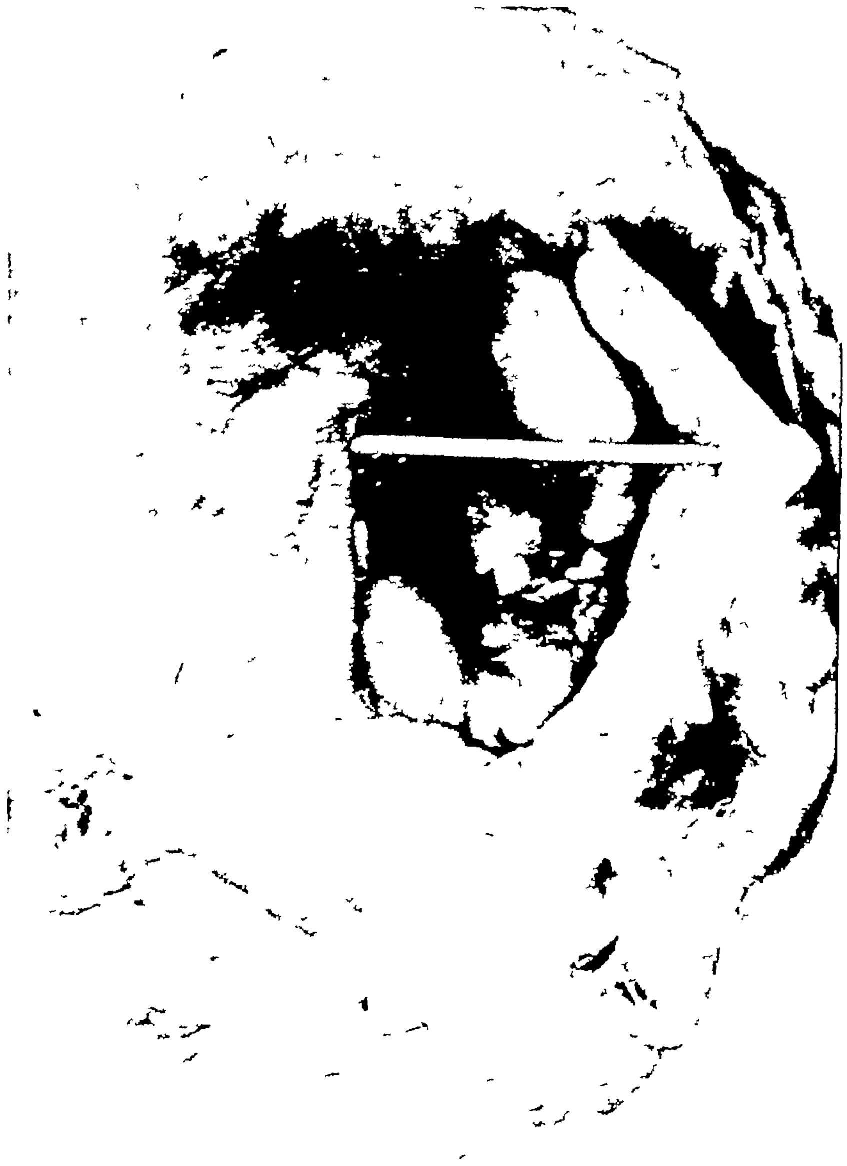

Fig 1 Case 2 Autopsy specimen Sagittal section shows extension of prostatic neoplasm into bladder

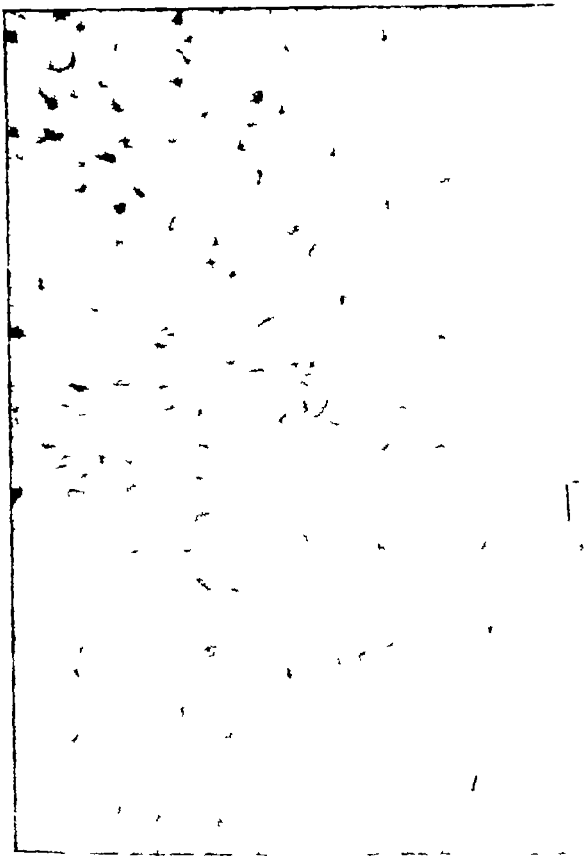

FIG 2 Case 2 Photomicrograph ×430

carcinoma diagnosed by rectal palpation Orchiectomy had been performed elsewhere Symptomatic and local response was excellent until August 1952, when he was referred to us because of nocturia and difficult urination Transurethral prostatic resection was performed on August 25, 1952 The tissue removed showed the typical scirrhous type of adenocarcinoma Postoperative response was satisfactory until late July 1953 when he complained of extreme nocturnal urgency and difficulty in voiding and a sensation of rectal obstruction The left prostatic lobe was only slightly enlarged, soft smooth and tense feeling The right lobe was very hard nodular and fixed but only slightly enlarged The median sulcus felt thickened when paplated over a urethral sound Acid phosphatase level was not elevated A second transurethral prostatic resection was performed on August 29, 1953 Microscopic study showed "a much more anaplastic appearance of the tumor cells with relative decrease in stroma in most sections" Following this the patient was able to urinate freely but complained of perineal pain In mid-November his urinary frequency increased rapidly and severe pyuria developed Cystoscopy was performed because of urinary retention A large rubbery piece of sloughed tissue was removed Another amount of tissue was interpreted as adherent slough in the prostatic urethra On December 12, a Foley catheter was inserted because of urinary retention Thereafter the patient was unable to void and on December 26 the "sloughing tissue" was removed from the prostatic cavity by further resection The slough covered only the surface The underlying tissue was almost white in color and very soft, cutting like soft cheese Note was made of the low vascularity of the tumor Microscopic report "Sections of prostate are largely replaced by tumor and large

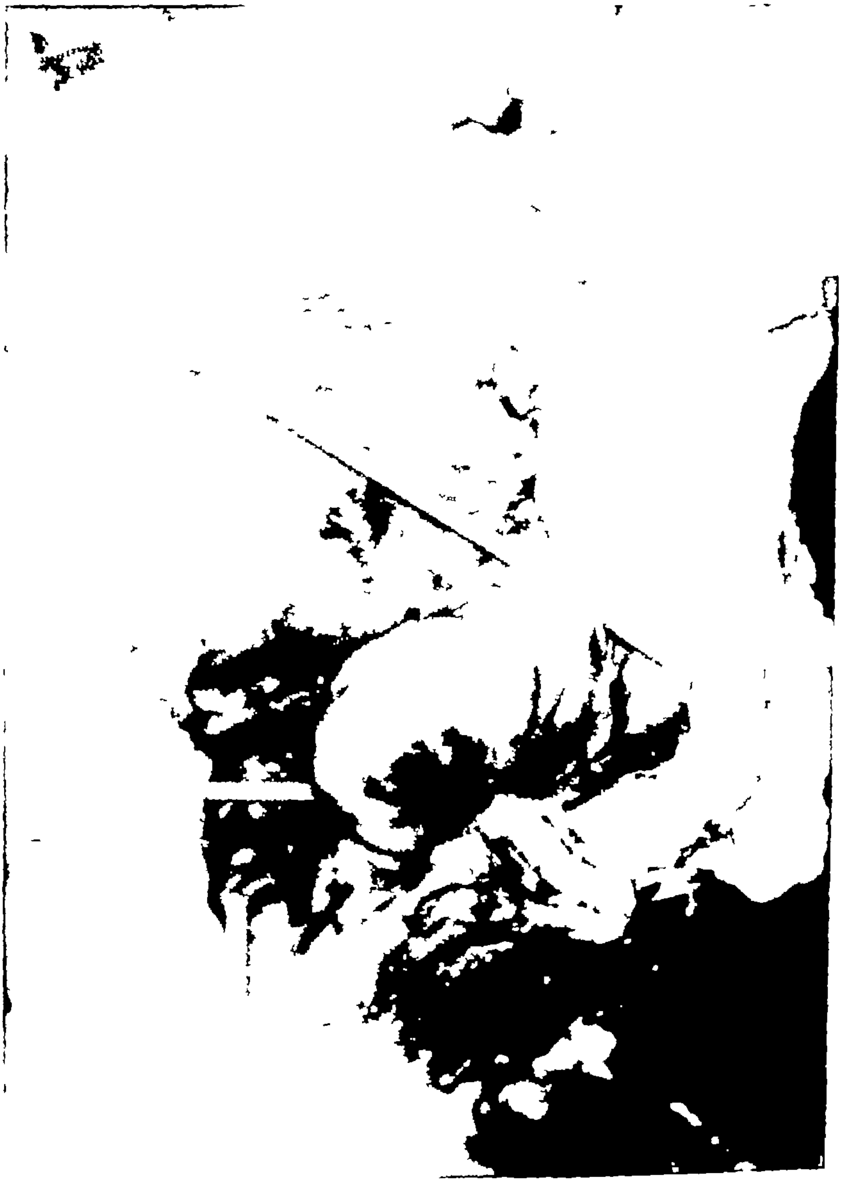

Fig 3 Case 3 Autopsy specimen Sagittal section showing extension of prostatic neoplasm into bladder

FIG 4 Case 3 Photomicrograph X430

areas of necrosis The tumor is highly anaplastic and forms no organoid structure The cells vary tremendously in size Many are small, containing a small hyperchromatic nucleus Others are extremely large containing abundant foamy cytoplasm and large bizarre nuclei It is not immediately obvious whether tumor changes represent carcinoma or sarcoma Many of the cells contain abundant granular cytoplasm and these cells resemble closely those of a granular cell myoblastoma Diagnosis Anaplastic malignancy of the prostate, possible myoblastoma The patient's condition deteriorated rapidly following this procedure and he died December 30, 1953 Autopsy diagnosis by Dr P T Dolan "Medullary anaplastic carcinoma of the prostate with regional lymphnode metastases" (figs 3 and 4)

DISCUSSION

It should be emphasized that the lesions here reported are variations of one kind of tumor, i e adenocarcinoma This kind of prostatic cancer varies from the commonly encountered hard nodular, fixed slowly-growing scirrhous type to the almost fluctuant, smooth fungating medullary type, with all the gradutions between these two extremes The cellular structure of the medullary tumor is much less differentiated and presents a much more malignant microscopic picture than does the scirrhous type Because of the very rapid proliferation in the medullary tumors, the tendency to formation of fibrous stroma is greatly reduced causing the extreme softness of this type of adenocarcinoma

Probably because of its lesser degree of cell differentiation, the medullary tumor shows less tendency to elevate serum acid phosphatase levels Theoretically, its resistance to estrogenic therapy may be due to decreased ability of estrogen to interfere with anaerobic respiration of the less differentiated cells of this type of neoplasm

SUMMARY

Soft varieties of prostatic carcinoma are of several types, all characterized by a rapidly fatal clinical course and physical findings so different from the usual scirrhous variety as to make preoperative diagnosis extremely difficult

Their softness is due to rapid, fungating cellular growth with minimal production of stroma

In the cases here reported as well as those observed by others, serum acid phosphatase was not elevated and hormonal therapy was not effective

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LIMITATIONS OF RADIOISOTOPE THERAPY FOR PROSTATIC CARCINOMA

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Radioactive gold and chromic phosphate have been widely publicized for the treatment of prostatic carcinoma which is without observable bony metastasis but is outside the prostatic capsule and hence beyond total surgical excision. On theoretic grounds and from assessment of the reported clinical results we question the therapeutic usefulness of these radioactive colloids.

The objective of cancer therapy may be eradication of the disease, "arrest" of growth or mere palliation. We should examine the value of the radiocolloids in this light.

ERADICATION

The patients for isotope therapy are usually chosen by excluding those with carcinoma entirely within the prostatic capsule (who are treated by radical prostatectomy). Therefore, by definition, tumor cells lie outside the prostate in the cases under consideration, having spread by extension through the capsule or by invasion of the perineural lymphatics and perhaps by vascular invasion as well. Lymphatic invasion, especially, is known to occur early in the disease.

For radioactive isotope therapy to be *curative*, it must destroy all the lesion within the prostate and also kill those cells already advancing outside the prostatic capsule. To accomplish this, the isotope must be placed around the periphery of involvement. Central injection of the tumor may be palliative but obviously cannot be curative unless the isotopic radiation extends into the periphery where it can cut off the routes of dissemination and destroy that spread which has already occurred.

Can the radiocolloid be so placed as to kill all the cancer cells? The answer will probably always be "no." This is indicated by the unequal distribution seen in the microscopic sections and radioautographs of biopsy specimens, and in radiographs taken with radiopaque media.[1, 2] The evidence is of random distribution rather than of precise placement. The periphery of the tumor lies high behind the bladder, in the seminal vesicles, in the lymphatic channels and in surrounding connective tissue, and receives the poorest pattern of radiation.

If the lymph channels would carry the radiocolloid to involved nodes, the chance for cure would be enhanced. Our work showed the distribution to be

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Read in part at annual meeting, American College of Surgeons, San Francisco, October 8-12, 1956.

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TABLE 1

	Living
	per cent
Flocks 1956 (gold, followed 4 years)	*34 0
Nesbit and Baum (non-metastatic cases followed 4 years)	
Both stilbestrol and orchiectomy	†53 9
Stilbestrol alone	33 5
Orchiectomy alone	37 7
No treatment	14 0
Ganem (same, followed 5 years)	
Both stilbestrol and orchiectomy	45 7

* May have had previous treatment

† No previous treatment

haphazard even in normal lymphatics[3] When the lymphatics are involved with, and probably blocked by, tumor, it would be very surprising indeed if the colloid reached the involved nodes in significant quantities O'Conor and co-workers[4] using radioactive gold, reported "No demonstrable radiation damage *could be detected in the regional lymphatic tissue [p 389]* " In their earlier experiments in dogs, using chromic phosphate,[1] however, there was some evidence of radiation effect in the regional lymph nodes

As for getting around the entire tumor, even Kerr, Flocks, and co-workers[5] now state, "Experience indicates, also, that it is practically impossible to sterilize any except the smallest neoplasms with radioactive material alone [p 640] "

What about the clinical results of this type of therapy? Here we can say little that is conclusive So far, the longest series (Flocks[6]) has gone only 4 years, with a steadily rising proportion of deaths A comparison of these results with the outcome after castration and/or estrogen therapy is helpful The figures in table 1, unfortunately, are not directly comparable, since Nesbit and Baum[7] date survival from the time of diagnosis, whereas Flocks uses the date of beginning gold therapy His were still relatively early cases, however Patients with treatment before gold therapy would, therefore, have lived longer with their cancer than the figures indicate The 4-year survival with non-metastatic prostatic carcinoma treated with estrogens and orchiectomy is 53 9 per cent[7] Ganem[8] found a 5-year survival of 45 7 per cent with combined therapy This is in contrast to the 34 per cent survival in the 4-year series of Flocks,[6] even if we remember that the series are not directly comparable Gold therapy is better than no treatment at all, since without therapy only 14 per cent survived 4 years

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ARREST OR PALLIATION

We are then left with isotope therapy merely as a method of arrest or palliation since we find little theoretical reason to expect cure of advanced prostatic carcinoma by the radiocolloids and no clinical evidence that any of these patients are cured Is isotope therapy as effective as anti-androgen therapy as a method of palliation? What are the complications and how frequently do they occur?

Bulkley, Cooper and O'Conor[4] in an open series of 34 cases, the longest followed 2½ years, reported 45 per cent improved by isotope injection plus estrogen therapy Fifty-five per cent either were not improved or died Of 12 patients treated with radioactive yttrium (which is non-colloidal), only 2 were improved Could you not expect a similar number of arrests from estrogens alone?

Rusche and Jaffe[9] followed 59 cases for 1 to 3 years after treatment by chromic phosphate injection plus transurethral resection of as much of the prostate as possible In this short-term series 66 per cent were improved and 34 per cent either were not improved or died The resection of the prostate may have played an important role in the improved patients Other series are small or have been followed too short a time for any evaluation [10, 11]

Regarding immediate complications, Flocks and co-workers[12] reported in 1952 that "rectal complications have become more severe than the first follow-up survey indicated These workers have subsequently been able to avoid most rectal changes[6] However would a new group have to go through the same trial period before gaining enough experience? Rusche and Jaffe,[9] using the suprapubic route for injection state "A severe local radiation reaction develops in the prostate area about 10 to 14 days after the initial suprapubic injection This reaction reaches a peak in about 4 to 6 weeks and gradually subsides over a period of 10 to 12 weeks During the peak of the reaction there is marked edema on rectal examination of the prostate area The patient usually complains of a moderate to severe degree of rectal pain for a few weeks, as well as frequency of urination due to bladder irritation Perineal injection apparently causes a less severe reaction" O'Conor and Bulkley [4] describing 5 patients treated with radioactive chromic phosphate had 2 deaths systemic radiation resulted in aplastic anemia.

Whether the patients are better off even after these immediate effects have subsided is difficult to determine from the available data Relatively fe[illegible] patients with spreading prostatic carcinoma have serious trouble from bleeding, infection, or obstruction, and in most instances their complications can be abated without the use of the radiocolloids They go downhill with bone and nerve pain, which the isotopes have not been shown to affect It is hard to find data in the writings of the advocates of isotope therapy regarding obstruction, renal function and urethral symptoms before and after treatment It is these effects of advancing prostatic carcinoma which must be shown to be better suppressed if palliation by isotopes is to be considered effective

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[10] Orr L M Campbell J L and Thomley M W Treatment of inoperable prostatic carcinoma by Au[illegible] J Urol 73 1063 1955

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[12] Flocks R H Kerr H D Elkins H B and Culp D Treatment of carcinoma of the prostate by interstitial radiation with radioactive gold [illegible] a preliminary report J Urol 68 510–522 1952

[4] O'Conor V J and Bulkley G J J Urol 77 [illegible] 1957

THE PLACE OF ISOTOPE THERAPY

The results so far available do not seem to justify the use of radioactive substances routinely in cases of non-metastatic late prostatic carcinoma The pioneers (Flocks and co-workers) choose lesions for treatment which are beyond cure by radical prostatectomy, yet they "now believe that complete eradication of the carcinoma by interstitial injection of radioactive gold is not feasible [p 638]"[5]

Perhaps its place is not for the patient with a late but limited lesion at all, but rather in the early case when radical surgery is not acceptable or in the late case with obstruction, in lieu of transurethral resection

The several competent groups now in the field should be encouraged to amplify their studies to tell us 1) whether the immediate painful effects can be regularly avoided, 2) whether transurethral resection of the prostate plus isotopes is statistically better for palliation than prostatic resection alone, and 3) whether antiandrogen therapy plus isotope injection is really more effective than antiandrogen therapy alone The metastasis of the cancer is not affected by isotope treatment, so we are left with the question Will these patients have easier deaths with fewer local complaints? Until such data are available, urologists might best be advised to use familiar measures, measures which they know to be effective

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BACTEREMIA AND SHOCK IN UROLOGY

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The frequent occurrence of bacteremia during and after urologic procedures is well known[1] [2] Operative and manipulative trauma to extremely vascular areas, often the locus of virulent micro-organisms, must produce bacterial invasion of the bloodstream far more often than it is recognized When the natural defense mechanism of the body is overwhelmed, the clinical picture of high temperature, hypotension and peripheral vascular collapse is seen Observation and management of several patients with this complication recently led the authors to consider the the pathogenesis of the syndrome, and to formulate a rational method of treatment

CASE REPORT

Case 1 I K (HUP No 001047), a 62-year-old man, entered the hospital in acute urinary retention He had increasing symptoms of prostatism for 3 years prior to admission A physician had catheterized him 24 hours prior to admission, but had withdrawn the catheter Upon admission, urinalysis showed many white blood cells per high power field, and the white blood cell count was 8,700/cu mm Other routine studies were not abnormal A transurethral resection was performed On the sixth postoperative day, a secondary hemorrhage occurred Transurethral fulguration was unsuccessful, and a suprapubic cystostomy was performed Within three hours, the patient's temperature rose to 106 4 degrees rectally The blood pressure dropped from 160/90 mm Hg to 100/60 mm Hg Intramuscular methoxamine, whole blood and nasal oxygen were started The patient had shaking chills, and appeared cold and clammy Three hours later, the blood pressure was 85/55 mm Hg Intravenous chlortetracycline and levarteranol were administered Twelve hours following this, the blood pressure was 80/40 mm Hg, the pulse rate was 90 per minute and weak The patient appeared disoriented A blood culture showed Aerobacter aerogenes, and the same organism was isolated from the urine The white blood cell count was 55,800/cu mm at this time Desoxycorticosterone acetate and cortisone were added to the therapeutic regimen Within 12 hours after administration of the steroid hormones, the patient's blood pressure stabilized between 110 and 120 mm Hg systolic, and it was possible to decrease the concentration of levarteranol In the next 24 hours, the patient was "weaned" from the vasopressors, and maintained a stable blood

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Read at annual meeting, North Central Section of American Urological Association Cleveland, Ohio, October 3-5, 1956

[1] Scott, W W Blood stream infections in urology, report of 82 cases J Urol, **21** 527, 1929

[2] Barrington, F J and Wright, H D Bacteremia following operations on the urethra J Path & Bact, **33** 871 1930

pressure without further support Oral antibiotics were begun, steroid thera discontinued, and the patient made a uneventful recovery

Case 2 N H (HUP No 074232), a 76-year-old man, entered Universi Hospital in acute urinary retention After catheter drainage for 5 days, urethr cystoscopy revealed a very vascular enlargement of the prostate gland, suggesti of neoplasm The white blood cell count was 7,300/cu mm and urinalys showed 7-10 white blood cells per high power field Repeated unsuccessful at tempts at catheterization produced much bleeding which necessitated a supr pubic cystostomy Twenty-four hours postoperatively the patient became di oriented, the rectal temperature was 105 6 degrees, blood pressure 80/60 mm Hg, and marked tachycardia developed Constant shaking chills and profu diaphoresis were noted Treatment with intravenous chloramphenicol and nas oxygen was begun Whole blood and intramuscular methoxamine did not corre the hypotension Intravenous phenylephrine and hydrocortisone were starte The temperature gradually returned to normal, and blood pressure was mai tained at 120-130 mm Hg for 24 hours on this regimen The vasopressors an steroids were gradually decreased, and oral medications started The patie recovered

Case 3 J B (No 70965), a 43-year-old woman, entered University Hospit with sharp right flank pain, frequency and urgency of 6 days' duration Bloo pressure was 205/120 mm Hg, temperature 99 degrees orally, and pulse 10 per minute Marked right costovertebral angle tenderness was present Whi blood count was 29,000/cu mm on admission, and urinalysis showed many whi blood cells per high power field An intravenous urogram showed an enlarge poorly functioning right kidney A ureteral catheter was passed to the right ren pelvis, and 25 cc of purulent urine was aspirated Following this a Johnso stone basket was used in an attempt to remove a suspected calculus This wa unsuccessful Twelve hours after this procedure the temperature rose to 10 degrees orally, and shortly afterward blood pressure was unobtainable Th patient was acutely disoriented, and had shaking chills Treatment with metho amine and intravenous phenylephrine failed to effect a sustained, measurabl blood pressure The white blood cell count rose to 59,000/cu mm Colifor organisms were isolated from the urine and the peripheral blood Intravenou levarterenol and chloramphenicol were started An electrocardiogram showe myocardial ischemia secondary to the hypotension Whole blood was added t the therapeutic regimen In the succeeding 72 hours, the patient was maintaine on levarterenol After several unsuccessful attempts were made to "wean" th patient from vasopressor agents intramuscular cortisone was begun Within 1 hours, the patient could be changed first to phenylephrine, then to methoxamin and 24 hours later was able to maintain her own blood pressure without support

DISCUSSION

The syndrome of bacteremia, hypotension and peripheral vascular collaps has been described and discussed by a number of investigators [3 6] Analysis of the

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[3] Ebert, R V, Borden, C W, Hall, W H and Gold, D A study of hypotension pro

various contributing factors and their relative importance is, as in all shock states, difficult Fine and his co-workers[7] [8] have stressed the bacterial factor in "irreversible shock," especially regarding its action on the vascular tree That an overwhelming infection may produce a picture of "cold hypotension" is well known, but studies on the mechanisms of such a syndrone are inconclusive Altemeier[9] reviews briefly the means by which infection might produce shock They might be categorized as follows

Mechanisms of Bacterial Shock

1 Direct action of bacteria and/or toxins upon capillary walls
2 Effect of a histamine like substance or protein degradation products of bacterial enzyme activity upon the vascular tree
3 Effect of bacterial toxins on medullary vasomotor centers or regional sympathetic ganglia
4 Action of toxins on the heart
5 Hemolysis, alteration of hemoglobin by bacteria or bacterial products contributing to hypoxia
6 Adrenal insufficiency produced by unknown mechanisms

It seems likely that each of these factors plays a role of varying importance in individual cases Another concept of irreversible shock is proposed by Shorr et al [10] who believe that VDM, a vasodepressor substance, is produced in excess by the hypoxic liver This causes further tissue anoxia and inability to combat infection on a normal metabolic level It has been shown that in the syndrome of shock and bacteremia there is hemoconcentration, a decreased blood volume, and disparity between the vascular space and extracellular fluid volume It is interesting to speculate on the therapeutic role of steroids in regard to the latter premise They may effect the extra- and intracellular electrolyte and osmotic relationships with resultant shift of intracellular fluids to the extracellular space This, in turn, may decrease the existing disparity between vascular space and blood volume Another possibility is that the steroids may potentiate vasopressor agents by affecting cell response

There is, unfortunately, no accurate laboratory data to prove that a state of adrenal insufficiency existed in these cases It is a clinical fact, however, that addition of adrenal steroids improved the clinical situation rapidly It is postulated that a chronic and severe stress situation existed, and that a state of

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[7] Fine, J, Frank H Schweinburg, F, Jacob, S and Gordon, T The bacterial factor in traumatic shock Ann N Y Acad Sci, 55 429 1952

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[9] Altemeier, W A Armed Forces Med Svc Grad Sch Symposium on Shock, May 1951

[10] Shorr E Zweifach, B W, Furchgott, R and Baez, S Hepato renal factors in circulatory hemostasis Circulation 3 42 1951

TABLE 1 *Treatment of bacteremia and shock*

Circulatory volume	Blood, iv fluids and electrolytes	According to Calculated Needs
Antibiotics	Chloramphenicol	IV—500 mg q 12 h
	Oxytetracycline	IV—500 mg q 12 h
	Tetracycline	IV—500 mg q 12 h
		IM—100 mg q 6 h
	Penicillin	IM—400,000 u bid
Vasopressors	Methoxamine	IM—10-30 mg
		IV—20-160 mg q 12 h
	Phenylephrine	IV—10-30 mg /1000 cc
	Levarteranol	IV—4-16 cc /1000 cc
Cardiac glycosides	Lanatoside	IV—0 4 mg × 3 doses
Adrenal support	Hydrocortisone	IV—100 mg q 12 h

temporary adrenal exhaustion resulted from it It is not likely that actual destruction of the adrenal tissue was responsible, for it has been shown experimentally that this is a rare occurrence [3]

No single therapeutic agent was able to combat the clinical catastrophe which was encountered The program which was found to be most satisfactory is outlined as follows (table 1)

1) *Blood and intravenous fluids* It is of utmost importance to restore and maintain the extracellular fluid volume If blood loss is a factor, there is no better therapy than replacement with whole blood Patients who have high temperatures lose tremendous amounts of fluid and electrolytes by diaphoresis and these must be restored Maintenance of an adequate fluid volume is a *sine qua non* of successful therapy

2) *Antibiotics* It has been found that the most rapid and effective way to reach and maintain adequate bacteriocidal and bacterostatic levels is to use intravenous broad spectrum antibiotics Chloramphenicol, 500 mg every 12 hours, has been most satisfactory Intramuscular penicillin, 400,000 units twice daily, is used as an adjuvant because of synergism Most of the organisms encountered were sensitive to this combination This is intended to combat bacterial invasion, and perhaps block further effect of bacterial toxins

3) *Vasopressor agents* Methoxamine (vasoxyl), phenylephrine (neo-synephrine), and levarteranol (levophed) have been necessary It has been thought best to begin therapy with methoxamine If this is unsuccessful, phenylephrine, 10–20 mg per 1000 cc dextrose is used intravenously If this fails, 4–16 cu cm of levarteranol per 1000 cu cm of intravenous fluid usually is able to maintain the blood pressure The patients may be weaned from the vasopressors in the reverse order, until their vascular tree is able to maintain sufficient tone to stabilize the blood pressure on its own

4) *Cardiac glycosides* In some cases, bacteremia produces toxic myocarditis with attendant heart failure Rapid digitalization is indicated by the intravenous route This complication, fortunately, did not occur in these cases

5) *Adrenal support* As just discussed, the mechanisms and etiology of adrenal

insufficiency in these cases are uncertain [11, 12] Addition of cortical steroids such as hydrocortisone 100 mg 1000 cu cm every 12 hours improved the clinical situation, and allowed gradual withdrawal of artificial means of supporting the blood pressure

SUMMARY

Shock associated with bacteremia is a real hazard in urologic procedures Three illustrative cases are presented

The pathogenesis of the syndrome is discussed and a program of management is outlined

Adrenocortical support appears to be vital to the recovery of some of these patients

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NISENTIL* IN UROLOGIC PROCEDURES
A REVIEW OF 1,003 CASES

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Analgesia for urethral instrumentation in the male, particularly in the presence of prostatism, and in the apprehensive female, usually leaves much to be desired unless supplemented or replaced by regional or general anesthesia This is because pain from distending the urethra in either sex, and from straightening it in the male is but little reduced by the topical application of any agent, no matter how potent This is due to shallow penetration by local anesthetics Much has been said about the importance of reassurance and gentleness, but these measures are ineffectual in patients who have previously been instrumented by heavy handed individuals, or in those who have had the misfortune to talk with those who have been so treated The use of regional or general anesthetics obviates this particular difficulty, but runs up costs by necessitating hospitalization and the payment of fees for anesthesia Impressed by the report of McCrea and Post that the intravenous injection of nisentil (dl-alpha-1,3-dimethyl-4-phenyl-4-propionoxy-piperidine hydrochloride) yielded satisfactory analgesia of prompt onset and short duration for cystoscopic examinations, we have used this drug in more than a thousand urologic procedures with considerable satisfaction to ourselves and, more particularly, to the patients

At first nisentil was given without any premedication, but produced an annoyingly high incidence of nausea It was next combined with a very small dose of a narcotic antagonist, however, it was found that the combination led to protracted drowsiness or fairly deep sleep which defeated our purpose (short analgesia which would permit the patient to leave shortly after the procedure) We next tried 50 mg dramamine given orally at the time of the patient's arrival, results were gratifying, and this regimen has since been used in the vast majority of the people in the series

Topical cocaine was used for all urethral instrumentation Four and one half grains (270 mg) of cocaine were freshly dissolved in 15 to 20 ml sterile distilled water, injected slowly and gently into the male urethra, and retained with a Hyams clamp Two cotton applicators dipped in 10 per cent cocaine and then in KY jelly were then inserted into the external urinary meatus In the female, one such applicator was inserted in the internal meatus and a second one was left in the mid urethra, nothing was injected

After ten to fifteen minutes the nisentil was given intravenously in 10 ml sterile normal saline Dose for the average adult was 30 mg , this was reduced to as little as 10 mg in feeble old men, and was increased to as much as 60 mg in robust individuals Divided doses were used not infrequently Because of the general feeling that the use of any respiratory depressant in young children is

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* Supplied through the courtesy of Dr M J Schiffrin of Hoffman LaRoche, Chicago

inadvisable, and because they are usually better handled under general anesthesia, we have had very little experience with the drug in such patients. We have used topical cocaine so long and hence are so familiar with its effects that its employment in conjunction with nisentil could hardly interfere with our assessment of the value of the latter.

As soon as the intended procedure had been completed, each subject received 0.3 gm. (5 grains) of caffeine sodium citrate (or a cup of strong coffee) orally to shorten the after effects of the narcotic. Patients were allowed to leave no sooner than 1½ hours after administration of the drug, preferably in the company of friends or relatives, or in a taxicab. However, the senior author was driven downtown by one of the patients starting 1¼ hours after he had received 30 mg. nisentil followed by a cystoscopic examination. He displayed no more than his usual contempt for oncoming and intersecting traffic.

Analgesia was considered "satisfactory" if the patient was comfortable during manipulation and experienced no untoward reactions. A few were listed as "fair" if they registered mild protests concerning discomfort or experienced slight reactions to the drug. Tabulated as "failures" were those who could not tolerate the proposed manipulation, and those who experienced reactions necessitating discontinuance of the procedure, or hospitalization thereafter. All judgments concerning the effectiveness of the analgesia were rendered by the physician making the cystoscopic examination or other procedure.

One reaction to the drug has not been listed nor tabulated because it is regarded as normal. It consists of mild dizziness coming on almost at once and subsiding within a few minutes. Some patients have compared its intensity to that following the rapid consumption of several Martinis.

RESULTS

Nine hundred and sixty-two patients, chiefly elderly men, underwent 1,003 urological procedures, the number and variety of the 945 successful ones being enumerated in table 1. The 58 cases listed as "miscellaneous" were distributed as follows: cystoscopic biopsy 13, ureteral catheterization 9, trocar cystostomy 6, fulguration of vesical neoplasm 4, aspiration of renal cyst 3, excision of ure-

TABLE 1. *Number of procedures with satisfactory analgesia*

Procedure	Number of Cases
Cystoscopy	493
Retrograde pyelography	160
Urethral dilatation	130
Needle biopsy of prostate	41
Cystoscopic overdistention of the bladder	33
Cystoscopic electrocoagulation of bleeding points and evacuation of clots	16
Ureteral dilatation	14
Miscellaneous	58
Total	945

thral caruncle 3, cystoscopic removal of foreign body or stone 4, urethrogram, vasectomy, and replacement of nephrostomy tube, 2 each, and circumcision, extraction of a fragment of urethral catheter, removal of sutures, meatotomy and extraction of urethral stones, drainage of abscesses of glans penis, removal of pack from wound, orchiectomy, litholapaxy, closure of urethral fistula, and aspiration of hydrocele, one each When tissues were to be cut, procaine was injected locally, the nisentil being used to allay apprehension and to reduce the intensity of the pain from the preliminary pricks of the needle

Nisentil produced satisfactory analgesia in 94 per cent of the 1003 procedures, 4 per cent being graded as failures, and 2 per cent as only fair Conditions responsible for the 46 failures follow analgesia was inadequate in 24, nausea occurred alone in 6 and with vomiting in 7 There were two instances of mild respiratory depression with slight cyanosis, both relieved by brief inhalation of oxygen, and neither interfering with the planned manipulation One occurred in a child of twelve, and the other in a man of 85, indicating that nisentil must be given cautiously in the extremes of life, just as is the case with any potent narcotic Two patients were quite lethargic for some time so that they had to be admitted to the hospital and thus were classed as failures Each of the following reactions was seen once nausea and vomiting combined with transitory disorientation, mild convulsive movements, muscular twitching a wheal at the site of injection, and a fleeting cocaine reaction (pallor, weakness, and tachycardia)

In our first 55 cases nisentil was supplemented by a narcotic antagonist but this regimen was abandoned in favor of preliminary medication with dramamine, and of postmanipulative administration of caffeine for reasons already mentioned

These observations confirm those of McCrea and Post, but in a larger group with a greater variety of procedures Nisentil appears to be a narcotic which can be used safely in the manner described to produce prompt analgesia of sufficient duration to permit the performance of a considerable variety of short and moderately painful manipulations without requiring confinement to the hospital Its safety is indicated by the fact that only two instances of mild respiratory depression were encountered in 1,003 trials, and that both disappeared after brief administration of oxygen Since the patients were 12 and 85 years of age, it is likely that a smaller dose in each instance would have served our purpose without altering respiration Narcotic antagonists were not only unnecessary, but exerted a synergistic action which deepened and prolonged analgesia unnecessarily

Criteria of failure were quite rigid in that the occurrence of side effects such as nausea and vomiting, which did not prevent performance of the intended manipulation, prompted us to classify the ensuing analgesia with the failures Allowing for this, successful analgesia was achieved in 97 per cent of the whole group

It should be emphasized that all procedures listed were performed in the cystoscopic rooms of the University Hospitals, where anesthesiologists and all equipment needed for resuscitation were available if needed It seems unwise to give nisentil for analgesia in very young children, both because of the susceptibility of their respiratory centers to narcotics, and because their co-operation cannot be secured It should not be used as an office procedure unless equipment for resuscitation is available, although it has not been really needed in our cases

SUMMARY

The use of nisentil for analgesia during urologic procedures has been described

In 1,003 trials in 962 patients it provided adequate analgesia in 97 per cent, and satisfactory analgesia without adverse reactions of any kind in 94 per cent

Its use appears, on the basis of our experience with it, to be safe, effective, and economical

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SECTION MEETINGS

Mid Atlantic—Hotel Jefferson, Richmond, Va., October 1–4 1958
Northeastern—White Face Inn White Face N Y September 8–11 1957
North Central—Grand Hotel Mackinac Island Mich August 28–30 1957
Southeastern—Hollywood Beach Hotel Fla., January 12–16 1958
Western—Olympic Hotel Seattle Wash May 27–30 1957
South Central—Oklahoma City Okla, October 21–24, 1957

The Deutsche Gesellschaft für Urologie will meet in Vienna during September 1957 Details may be obtained from Prof Dr C E. Alken, Univ Klinik Homburg, Saar

Note by editor A complete list of the executive committees of the various sections and a complete list of the officers and members of the executive committees of the various branch societies will be printed in the December 1957 issue

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